to Claims 1 to 5.

13. Use of quinolone- and naphthyridone-carboxylic acid derivatives according to Claims 1 to 5 in the production of medicaments for the control of infectious diseases.

14. A commercial package comprising a compound according to any one of claims 1 to 5 together with instructions for the use thereof in the treatment of an infectious disease.

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OTTAWA, CANADA

PATENT AGENTS

or CH_2CH_2-CN,

in which

R' denotes hydrogen or C_1-C_3-alkyl,

or with a Michael acceptor such as dialkyl acetylenedicarboxylate, alkyl propiolate or a compound of the formula (IV)

$$CH_2=CH-R^5 \qquad (IV)$$

in which

R^5 represents $COCH_3$, CO_2R' or CN.

9. Quinolone- and naphthyridone-carboxylic acid derivatives according to Claims 1 to 5 for controlling diseases.

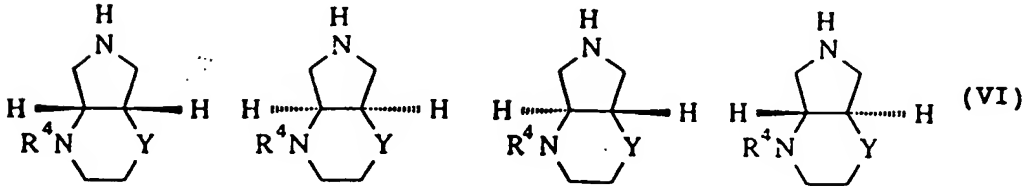
10. Quinolone- and naphthyridone-carboxylic acid derivatives according to Claims 1 to 5 for controlling infectious diseases.

11. Medicaments containing quinolone- and naphthyridone-carboxylic acid derivatives according to Claims 1 to 5.

12. Antibacterial agents containing quinolone- and naphthyridone-carboxylic acid derivatives according

X^2 represents halogen, in particular fluorine or chlorine,

are reacted with enantiomerically pure compounds of the formulae (VI)



(VI)

in which

Y represents O or CH_2 and

R^4 represents H or C_1-C_3-alkyl,

if appropriate in the presence of acid scavengers,

and the reaction product is optionally further reacted with a compound of the formula (IIIa)

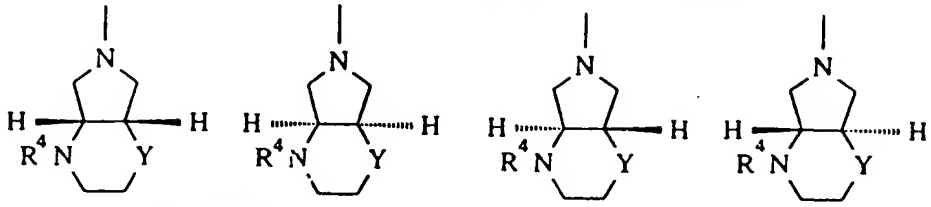
$$R^4\text{-}X^3 \qquad \text{(IIIa)}$$

in which

X^3 has the abovementioned meaning and

R^4 represents C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, $CH_2CH_2CO_2R'$

B represents a radical of th formulae,



(VI)

in which

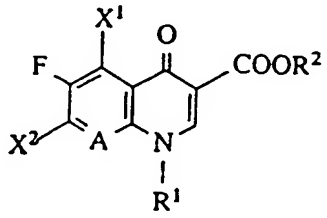
Y represents O or CH_2

R^4 represents H, C_1-C_3-alkyl, C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C-CO_2R', -CH=CH-CO_2R' or CH_2CH_2-CN or represents 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

in which

R' denotes hydrogen or C_1-C_3-alkyl,

characterised in that compounds of the formula (V)



(V)

in which

A, R^1, R^2 and X^1 have the abovementioned meaning and

A, Y, X^1, R^1 and R^2 have the abovementioned meaning,

is reacted with a Michael acceptor such as dialkyl acetylenedicarboxylate, alkyl propiolate or a compound of the formula (IV)

$$CH_2=CH-R^5 \qquad (IV)$$

in which

R^5 represents $COCH_3$, CO_2R' or CN.

8. Process for the preparation of quinolone- and naphthyridone-carboxylic acid derivatives according to Claims 1 to 3 of the formula (I) in which

A represents CH, CF, CCl, C-OCH_3, C-CH_3 or N,

X^1 represents H, halogen, NH_2 or CH_3

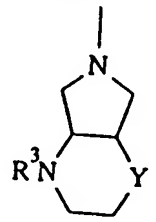
R^1 represents C_1-C_3-alkyl, FCH_2CH_2-, cyclopropyl or phenyl which is optionally monosubstituted to trisubstituted by halogen, or A and R^1 together can denote a bridge of the structure C-O-CH_2-$CH(CH_3)$-,

R^2 represents H, C_1-C_3-alkyl which is optionally substituted by hydroxyl, halogen or amino or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

C-O-CH_2-$CH(CH_3)$-,

R^2 represents H, C_1-C_3-alkyl which is optionally substituted by hydroxyl, halogen or amino or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl, and

B represents a radical of the formula



in which

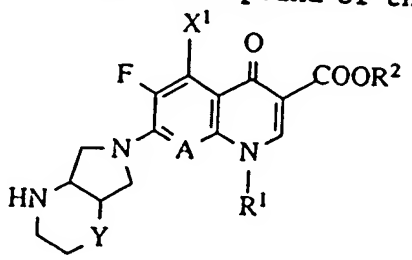
Y represents O or CH_2 and

R^3 represents CH_2CH_2-CO-CH_3, CH_2CH_2-CO_2R', $R'O_2C$-CH=C(CO_2R')-, -CH=CH-CO_2R' or CH_2CH_2-CN,

in which

R^1 denotes hydrogen or C_1-C_3-alkyl,

characterised in that a compound of the formula (II)



(II)

in which

in which

A, Y, X^1, R^1 and R^2 have the abovementioned meaning, is reacted with a compound of the formula (III)

$$R^3\text{-}X^3 \qquad \text{(III)}$$

in which

R^3 has the abovementioned meaning, and

X^3 represents halogen, in particular chlorine, bromine or iodine,

if appropriate in the presence of acid binders.

7. Process for the preparation of quinolone- and naphthyridone-carboxylic acid derivatives according to Claims 1 to 3 of the formula (I)

in which

A represents CH, CF, CCl, C-OCH_3, C-CH_3 or N,

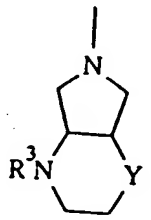
X^1 represents H, halogen, NH_2 or CH_3,

R^1 represents C_1-C_3-alkyl, FCH_2CH_2-, cyclopropyl or phenyl which is optionally monosubstituted to trisubstituted by halogen, or A and R^1 together can denote a bridge of the structure

can d note a bridg of the structure C-O-CH_2-$CH(CH_3)$-,

R^2 represents H, C_1-C_3-alkyl which is optionally substituted by hydroxyl, halogen or amino or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl, and

B represents a radical of the formula



in which

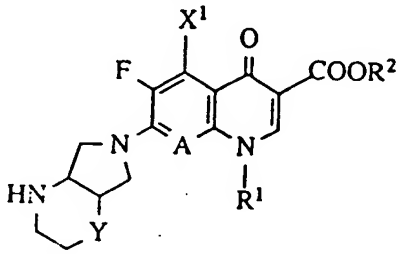
Y represents O or CH_2 and

R^3 represents C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, CH_2CH_2-CO_2R' or CH_2CH_2-CN,

in which

R' denotes hydrogen or C_1-C_3-alkyl,

characterised in that a compound of the formula (II)



(II)

5. Quinolonecarboxylic acids of the group consisting of

1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3 quinolinecarboxylic acid,

1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-5,6,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

and salts thereof.

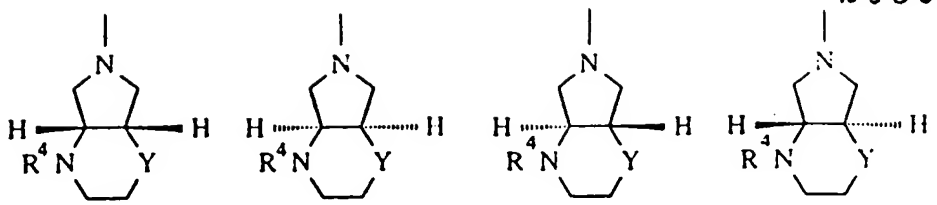
6. Process for the preparation of quinolone- and naphthyridone-carboxylic acid derivatives according to Claims 1 to 3 of the formula (I)

in which

A represents CH, CF, CCl, C-OCH_3, C-CH_3 or N,

X^1 represents H, halogen, NH_2 or CH_3

R^1 represents C_1-C_3-alkyl, FCH_2CH_2-, cyclopropyl or phenyl which is optionally monosubstituted to trisubstituted by halogen, or A and R' together



in which

Y represents O or CH_2 and

R^3 represents CH_2-CO-CH_3, CH_2-CO-C_6H_5, CH_2CH_2-CO-CH_3, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C-CO_2R', -CH=CH-CO_2R' or CH_2CH_2-CN,

in which

R' denotes C_1-C_2-alkyl,

and pharmaceutically utilisable hydrates and acid addition salts thereof and the alkali metal, alkaline earth metal, silver and guanidinium salts of the underlying carboxylic acids.

4. 8-chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid and pharmaceutically utilisable hydrates and acid addition salts thereof and the alkali metal, alkaline earth metal, silver and guanidinium salts of the underlying carboxylic acids.

R^4 represents H, C_1-C_3-alkyl, 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl, CH_2-CO-CH_3, CH_2-CO-C_6H_5, CH_2CH_2-CO-CH_3, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C(CO_2R')-, -CH=CH-CO_2R' or CH_2CH_2-CN,

in which

R' denotes C_1-C_2-alkyl,

and pharmaceutically utilisable hydrates and acid addition salts thereof and the alkali metal, alkaline earth metal, silver and guanidinium salts of the underlying carboxylic acids.

3. Quinolone- and naphthyridone-carboxylic acid derivatives of the formula (I) according to Claim 1, in which

A represents CH, CF, CCl, C-OCH_3 or N,

X^1 represents H, F, Cl, Br, NH_2 or CH_3,

R^1 represents C_2H_5, cyclopropyl or 2,4-difluorophenyl, or A and R^1 together can denote a bridge of the structure C-O-CH_2-$CH(CH_3)$-,

R^2 represents H, CH_3, C_2H_5 or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

B represents a radical of the formulae

2. Quinolone- and naphthyridone-carboxylic acid derivatives of the formula (I) according to Claim 1, in which

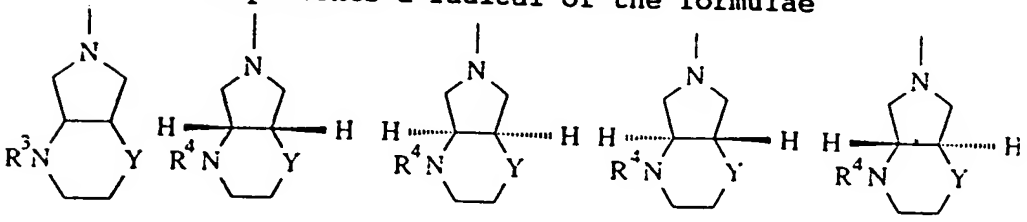
A represents CH, CF, CCl, C-OCH_3 or N,

X^1 represents H, F, Cl, Br, NH_2 or CH_3,

R^1 represents C_2H_5, cyclopropyl or 2,4-difluorophenyl, or A and R^1 together can denote a bridge of the structure C-O-CH_2-CH(CH_3)-,

R^2 represents H, CH_3, C_2H_5 or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

B represents a radical of the formulae

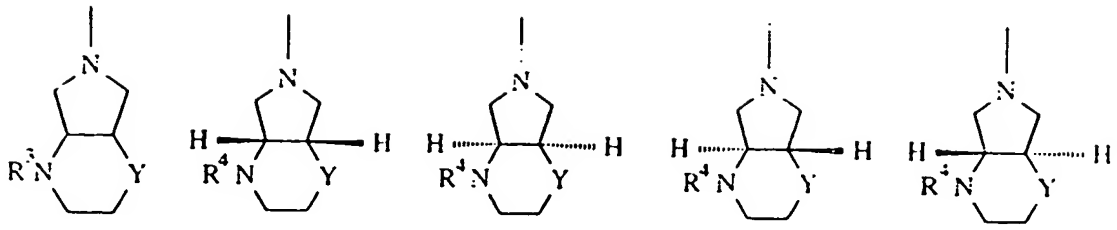


in which

Y represents O or CH_2 and

R^3 represents CH_2-CO-CH_3, CH_2-CO-C_6H_5, CH_2CH_2-CO-CH_3, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C(CH_3)-CO_2R', -CH=CH-CO_2R' or CH_2CH_2-CN,

in which R' denotes C_1-C_2-alkyl,



in which

Y represents O or CH_2 and

R^3 represents C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C-CO_2R', -CH=CH-CO_2R' or CH_2CH_2-CN,

in which

R' denotes hydrogen or C_1-C_3-alkyl,

R^4 represents H, C_1-C_3-alkyl, 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl, C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C-CO_2R', -CH=CH-CO_2R' or CH_2CH_2-CN,

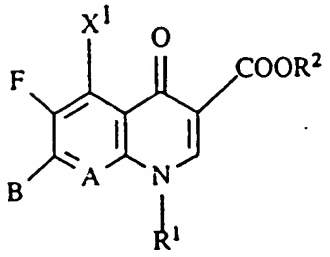
in which

R' denotes hydrogen or C_1-C_3-alkyl

and pharmaceutically utilisable hydrates and acid addition salts thereof and the alkali metal, alkaline earth metal, silver and guanidinium salts of the underlying carboxylic acids.

Patent Claims

1. Quinolone- and naphthyridone-carboxylic acid derivatives of the formula (I)



(I)

in which

A represents CH, CF, CCl, C-OCH_3, C-CH_3 or N,

X^1 represents H, halogen, NH_2 or CH_3,

R^1 represents C_1-C_3-alkyl, FCH_2CH_2-, cyclopropyl or phenyl which is optionally monosubstituted to trisubstituted by halogen, or A and R^1 together can denote a bridge of the structure C-O-CH_2-$CH(CH_3)$-,

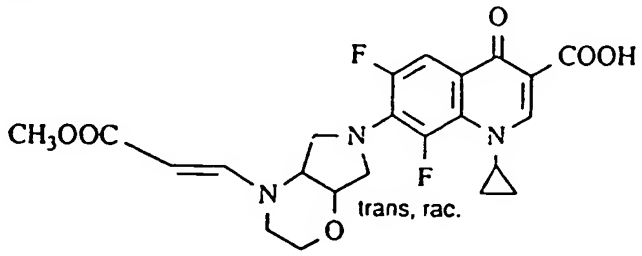
R^2 represents H, C_1-C_3-alkyl which is optionally substituted by hydroxyl, halogen or amino or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

B represents a radical of the formulae

Example 36 and 1-cyclopropyl-7-[5-(trans-2-ethoxy-carbonyl-vinyl]-trans-2-oxa-5,8-diaza[4.3.0]non-8-yl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid is obtained.

Melting point: 266-268°C (with decomposition) (from glycol monomethyl ether).

Example 56



1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(trans-2-oxa-5,8-diaza[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid is reacted with methyl propiolate analogously to Example 36 and 1-cyclopropyl-7-[5-(trans-2-methoxy-carbonyl-vinyl)-trans-2-oxa-5,8-diaza[4.3.0]non-8-yl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid is obtained.

Melting point: 275-277°C (with decomposition).

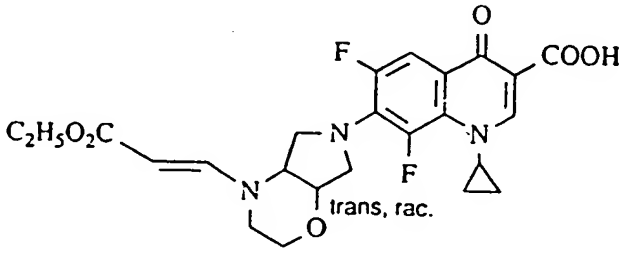
818 mg (2 mmol) of 1-cyclopropyl-5,6,8-trifluoro-1,4-dihydro-7-(1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid (from Example 13B) are treated with 680 mg (4 mmol) of diethyl acetylenedicarboxylate in 15 ml of ethanol and the mixture is treated in an ultrasonic bath at 30°C for 1 hour. The suspension is filtered off with suction, and the precipitate is washed with ethanol and dried at 70°C in a high vacuum.

Yield: 890 mg (77 % of theory) of 1-cyclopropyl-7-[5-(1,2-bis-ethoxycarbonyl-vinyl)-1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl]-5,6,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

Melting point: 220-222°C (with decomposition) (from glycol monomethyl ether)

$[\alpha]_d^{25}$: -57° (c=0.5, $CHCl_3$).

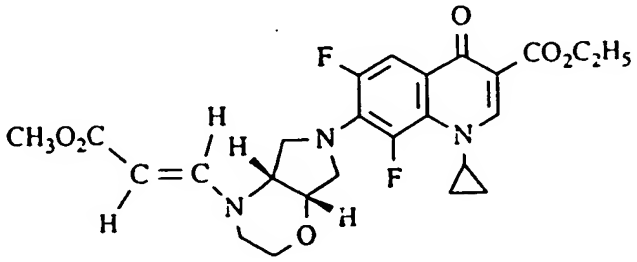
Example 55



The reaction is carried out with 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(trans-2-oxa-5,8-diaza[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid analogously to

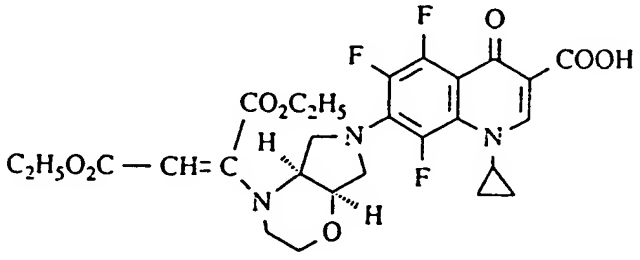
vinyl)-1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl]-4-oxo-3-quinolinecarboxylic acid of melting point 158-160°C (with decomposition) is obtained (from isopropanol):
$[\alpha]_D^{28}$: +8° (c = 0.27, $CHCl_3$).

Example 53

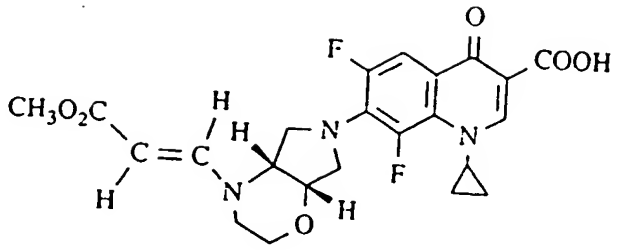


Reaction is carried out with the compound from Example 17 analogously to Example 36 and methyl 1-cyclopropyl-7-[2-(trans-2-ethoxycarbonyl-vinyl)-1S,6S-2,8-diazabicyclo[4.3.0]non-8-yl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate of melting point 168-169°C is obtained.

Example 54



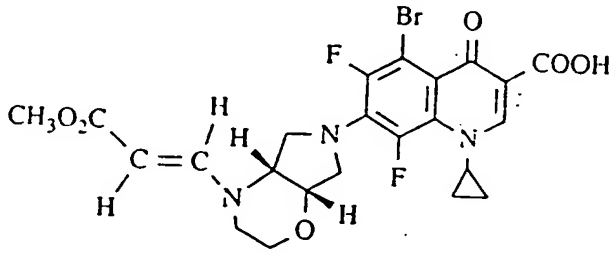
Example 51



Reaction is carried out with the compound from Example 10E analogously to Example 49 and 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-[5-(trans-2-methoxycarbonyl-vinyl)-1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl]-4-oxo-3-quinolinecarboxylic acid of melting point 230-234°C (with decomposition) is obtained (from glycol monomethyl ether);

$[\alpha]_D^{28}$: -27° (c = 0.5, $CHCl_3$).

Example 52



Reaction is carried out with the compound from Example 24 analogously to Example 49 and 5-bromo-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-[5-(trans-2-methoxycarbonyl-

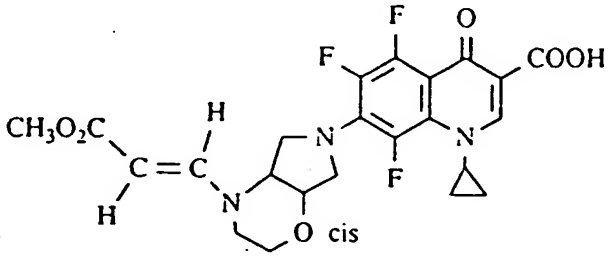
4-oxo-3-quinolinecarboxylic acid (from Exampl 11E) are heated und r reflux for 1 hour with 210 mg (2.5 mmol) of methyl propiolate in 10 ml of methanol. The mixture is concentrated and the isolated crude product (450 mg) is recrystallised from 4 ml of acetonitrile.

Yield: 8-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[5-(trans-2-methoxycarbonyl-vinyl)-1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl]-4-oxo-3-quinolinecarboxylic acid,

Melting point: 153-156°C (with decomposition),

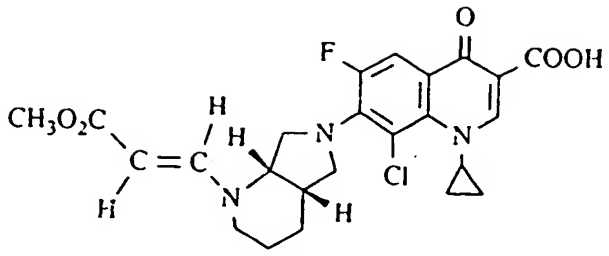
$[\alpha]_D^{28}$: +36° (c = 0.5, $CHCl_3$).

Example 50



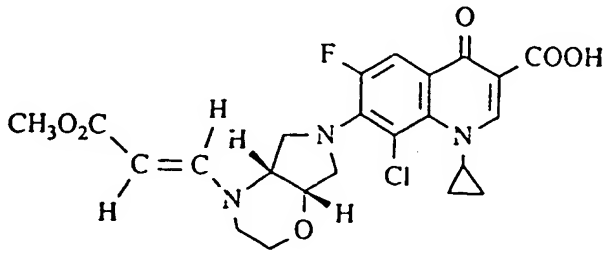
Reaction with the compound of Example 13A is carried out analogously to Example 49 and 1-cyclopropyl-5,6,8-trifluoro-1,4-dihydro-7-[5-(trans-2-methoxycarbonyl-vinyl)-cis-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl]-4-oxo-3-quinolinecarboxylic acid of melting point 169-170°C (with decomposition) is obtained (from glycol monomethyl ether).

Example 48



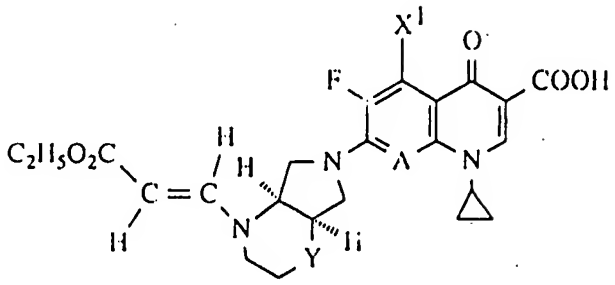
8-Chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid is reacted with methyl propiolate in ethanol or methanol analogously to Example 36 and 8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-[2-(trans-2-methoxycarbonyl-vinyl)-[S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid of melting point 220-222°C (with decomposition) is obtained, $[\alpha]_D^{24}$: +8.2° (c = 0.5, $CHCl_3$).

Example 49

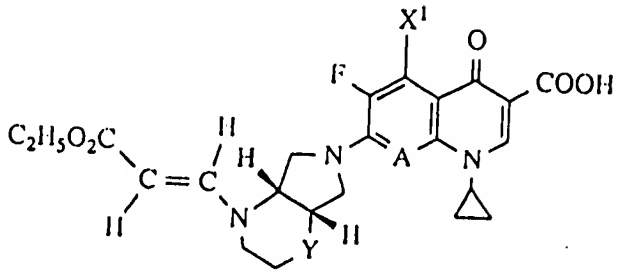


407.5 g (1 mmol) of 8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-

Analogously to Example 10, the following are obtained from the corresponding intermediate products:



Example	Starting material (example)	A	X^1	Y	Melting point [°C]	$[\alpha]_D$
45	10C	CF	H	O	208-209	+24° (c=0,5, $CHCl_3$)
46	11C	CCl	H	O	197-199	-46° (c=0,5, $CHCl_3$)
47	13B	CF	F	O	230-232	-5° (c=0,25, $CHCl_3$)



Example	Starting material (example)	A	X^1	Y	Melting point [°C]	$[\alpha]_D$
37	2A	CCl	H	CH_2	211-213	+6,3° (c=0,5, $CHCl_3$)
38	22	CH	CH_3	CH_2	199-201	-205° (c=0,5, $CHCl_3$)
39	3A	CH	H	CH_2	284-286	-231° (c=0,5, $CHCl_3$)
40	5	CF	NH_2	CH_2	246-248	-14° (c=0,5, $CHCl_3$)
41	6	N	H	CH_2	219-221	-162° (c=0,25, $CHCl_3$)
42	19	C-OCH_3	H	CH_2		-23° (c=0,25, $CHCl_3$
43	13C	CF	F	O	232-233	+8° (c=0,5, $CHCl_3$)
44	1A	CF	H	CH_2	225-227*)	

*)not recrystallised

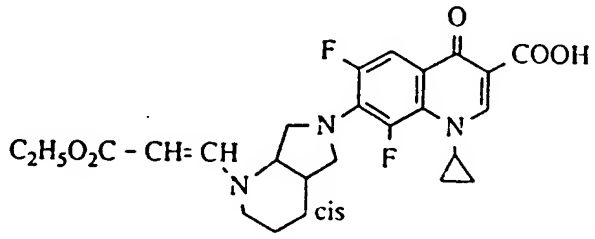
Melting point: 244-246°C.

Analogously to Example 36, the following are obtained from the corresponding starting materials:

The product from Exampl 2A is reacted with dimethyl acetyl nedicarboxylat analogously to Example 34. 8-Chloro-1-cyclopropyl 7-[2-(1,2-bis-methoxycarbonyl-vinyl)-1S,6S-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of melting point 210-212°C (with decomposition) is obtained in 87 % yield;

$[\alpha]_D^{24}$: +16.6° (c = 0.5, DMF).

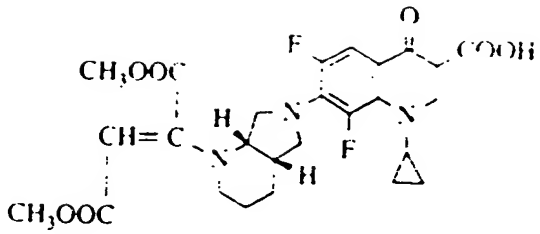
Example 36



780 mg (2 mmol) of 1-cyclopropyl-7-(cis-2,8-diazabicyclo-[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-oxo-3-quinolinecarboxylic acid are heated under reflux for 1 hour with 500 mg (5 mmol) of ethyl propiolate in 15 ml of ethanol. The suspension is cooled, and the precipitate is filtered off with suction, washed with 25 ml of ethanol and dried at 80°C in a high vacuum.

Yield: 880 mg (90 % of theory) of 1-cyclopropyl-7-[2-(trans-2-ethoxycarbonylvinyl)-cis-2,8-diazabicyclo-[4.3.0]non-8-yl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

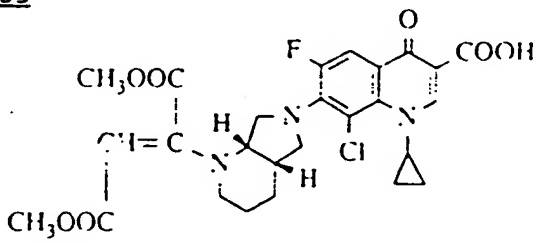
Example 34



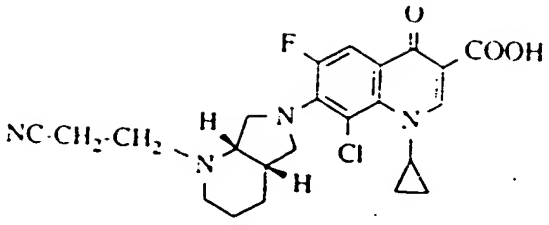
1.95 g (5 mmol) of the product from Example 1A are heated under reflux for 2 hours with 1.2 g (8 mmol) of dimethyl acetylenedicarboxylate in 50 ml of ethanol. The suspension is concentrated, the residue is stirred with water, and the precipitate is filtered off with suction and dried. The crude product (2.3 g) is recrystallised from glycol monomethyl ether/dimethylformamide.

Yield: 2 g (74 % of theory) of 1-cyclopropyl-7-[2-(1,2-methoxycarbonyl-vinyl)-1S,6S-2,8-diazabicyclo[4.3.0]non-8-yl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,
Melting point: 262-264°C (with decomposition);
$[\alpha]_D^{24}$: +28.8° (c = 0.24, CH_2Cl_2).

Example 35



Example 33

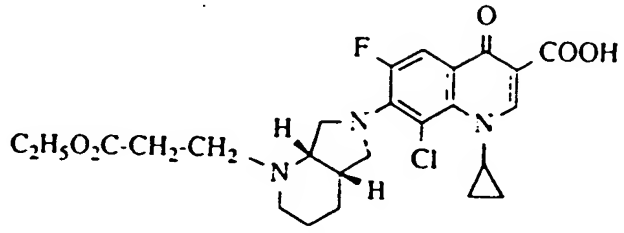


1.95 g (4.8 mmol) of the product from Example 2A are heated under reflux for 5 hours with 0.8 g (15 mmol) of acrylonitrile in 30 ml of ethanol. The mixture is evaporated, and the residue is stirred with water, dried (crude yield: 1.9 g) and recrystallised from glycol monomethyl ether.

Yield: 1.6 g (73 % of theory of 8-chloro-7-([S,S]-2-[2-cyanoethyl]-2,8-diazabicyclo[4.3.0]non-8-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,
Melting point: 153-155°C (with decomposition),
$[\alpha]_D^{27}$: -98.6° (c = 0.53, DMF),
Purity: 96 % strength (HPLC),
Mass spectrum: m/e 458 (M^+), 250, 149 (100 %, $C_9H_{13}N_2$), 110, 49.

oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-3-quinolinecarboxylic acid,
Melting point: 188-189°C (with decomposition).

Example 32



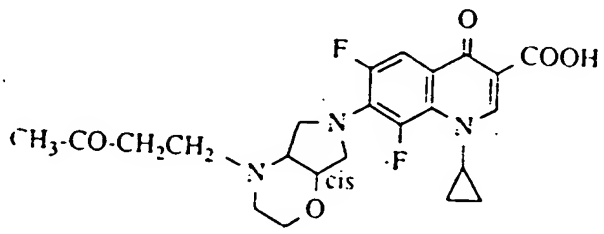
1.95 g (4.8 mmol) of the product from Example 2A are heated under reflux for 2 hours with 3 g (30 mmol) of ethyl acrylate in 30 ml of glycol monomethyl ether. The mixture is evaporated, the residue is stirred with water, and the precipitate is filtered off with suction, dried (Crude yield: 1.9 g) and recrystallised from glycol monomethyl ether.

Yield: 1.45 g (60 % of theory) of 8-chloro-1-cyclopropyl-7-([S,S]-2-[2-ethoxy-carbonyl-ethyl]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,
Melting point: 117-118°C (with decomposition),
$[\alpha]_D^{28}$: -103.5° (c = 0.49, DMF),
Purity: 99.6 % strength (HPLC).

80°C/15 mbar, and the oily residue is stirred with water until it solidifies. The solid product is filtered off with suction, washed with water and recrystallised from glycol monomethyl ether.

Yield: 830 mg (47 % of theory) of 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(cis-5-[2-oxopropyl]-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-3-quinolinecarboxylic acid,
Melting point: 192-193°C (with decomposition).

Example 31



1.56 g (4 mmol) of the product from Example 10A are heated under reflux for 3 hours with 1.8 g (25.6 mmol) of methyl vinyl ketone in 50 ml of ethanol. The suspension is concentrated at 70°C/12 mbar, and the residue is stirred with water and recrystallised from glycol monomethyl ether.

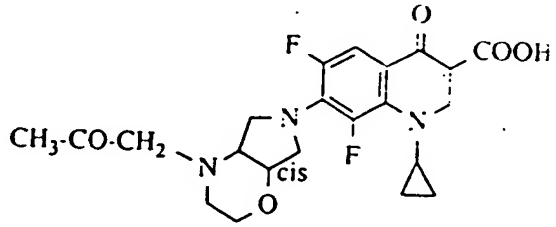
Yield: 1.33 g (72 % of theory) of 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(cis-5-[3-oxo-1-butyl]-2-

A. The product from Example 2A is reacted analogously to Example 27 and 8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-([S,S]-2-[3-oxo-1-butyl]-2,8-diazabicyclo[4.3.0]non-8-yl)-3-quinolinecarboxylic acid of melting point 107-109°C is obtained.

$[\alpha]_D^{23}$: -53° (c = 0.67, $CHCl_3$),
Purity: 99.2 % strength (HPLC).

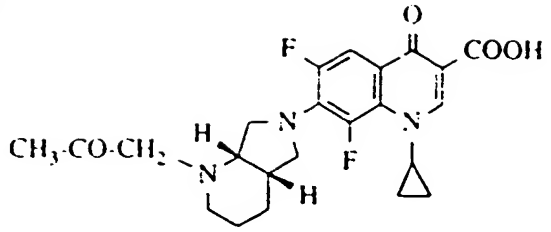
B. Rac. 8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-cis-2-[3-oxo-1-butyl]-2,8-diazabicyclo[4.3.0]-non-8-yl)-3-quinolinecarboxylic acid of melting point 124-125°C is obtained analogously using 8-chloro-1-cyclopropyl-7-(cis-2,8-diazabicyclo[4.3.0]-non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid.

Example 30



1.56 g (4 mmol) of the product from Example 10A are treated with 0.82 g (8.8 mol) of chloroacetone and 1.05 g (10.4 mmol) of triethylamine in 30 ml of dimethyl-formamide and the mixture is heated at 50-80°C for 3 hours. The yellow solution obtained is concentrated at

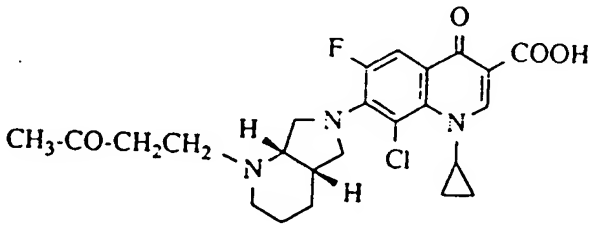
Exampl 28



1.95 g (5 mmol) of the product from Example 1A are heated at 50-80°C for 3 hours with 1.0 g (10.8 mmol) of chloroacetone and 1.3 g (13 mmol) of triethylamine in 30 ml of dimethylformamide. The solution is concentrated, the residue is stirred with water (pH 6), and the undissolved precipitate is filtered off with suction, washed with water and dried at 100°C in a recirculating air drying oven (crude yield: 1.3 g) and recrystallised from glycol monomethyl ether:

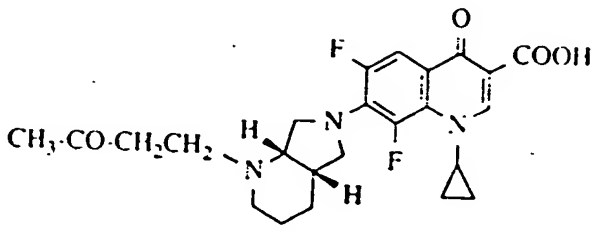
Yield: 1.12 g (50 % of theory) of 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-([S,S]-2-[2-oxopropyl]-2,8-diazabicyclo[4.3.0]]non-8-yl)-3-quinolinecarboxylic acid,
Melting point: 181-184°C (with decomposition),
$[\alpha]_D^{23}$:-72° (c = 0.55, $CHCl_3$).

Example 29



quinolinecarboxylic acid hydrochloride,
melting point: 258-260°C (with decomposition),
$[\alpha]_D^{25}$: +213.8° (c=1, H_2O).

Example 27



1.95 g (5 mmol) of the product from Example 1A are heated under reflux for 4 hours with 2.1 g (30 mmol) of methyl vinyl ketone in 50 ml of ethanol. The mixture is concentrated, the residue is stirred with water, and the precipitate is filtered off with suction, washed with ethanol and dried at 100°C/12 mbar.

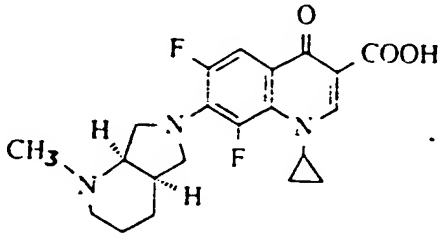
Yield: 2.1 g (91.5 % of theory) of 1-cyclopropyl-6,8-difluoro-1,4-dihydro-oxo-7-([S,S]-2-[3-oxo-1-butyl]-2,8-diazabicyclo[4.3.0]non-8-yl)-3-quinolinecarboxylic acid,
Melting point: 181-183°C (with decomposition)
(recrystallised from glycol monomethyl ether,
$[\alpha]_D^{24}$:-120.7° (c = 0.57, CH_2Cl_2)

Analogously to Example 1, the following ar obtained using [S,S]-2-methyl-2,8-diazobicyclo[4.3.0]nonane:

A: 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-([S,S]-2-methyl-2,8-diazobicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid,
melting point: 230-233°C (with decomposition) (recrystallised from glycol monomethyl ether);

B. 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-([S,S]-2-methyl-2,8-diazobicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid hydrochloride,
melting point: 258-260°C (with decomposition),
$[\alpha]_D^{25}$: -216.3° (c=1, H_2O).

Example 26

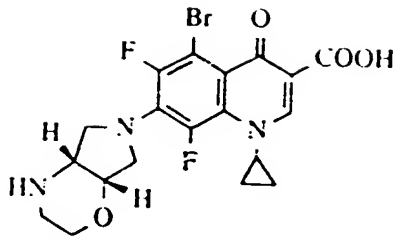


Analogously to Example 1, the following are obtained using [R,R]-2-methyl-2,8-diazabicyclo[4.3.0]nonane:

A: 1-Cycopropyl-6,8-difluoro-1,4-dihydro-7-([R,R]-2-methyl-2,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid,
melting point: 228-230°C (with decomposition) (recrystallised from glycol monomethyl ether):

B: 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-([R,R]-2-methyl-2,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-

Example 24



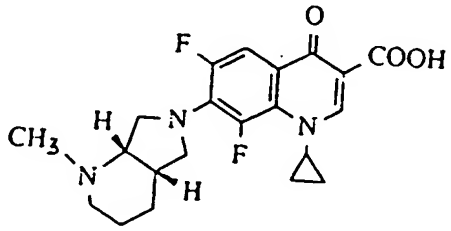
362 mg (1 mmol) of 5-bromo-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are heated under reflux for 1.5 hours with 220 mg (2 mmol) of 1,4-diazabicyclo[2.2.2]octane and 220 mg (1.1 mmol) of 1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]nonane dihydrochloride in a mixture of 3 ml of acetonitrile and 1.5 ml of dimethylformamide. The suspension is cooled, and the precipitate is filtered off with suction, stirred with 30 ml of water and dried at 90°C in a high vacuum.

Yield: 320 mg (68 % of theory) of 5-bromo-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid,

Melting point: 263-264°C (with decomposition),

$[\alpha]_D^{30}$: +251° (c = 0.3, CH_2Cl_2].

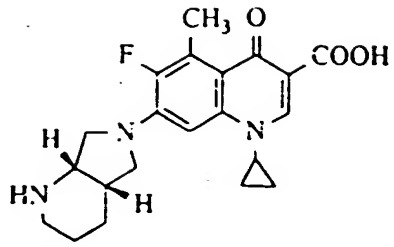
Example 25



A. 837 mg (3 mmol) of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid are heated under reflux for 2 hours with 1.1 g (10 mmol) of 1,4-diazabicyclo[2.2.2]octane and 665 mg (3.3 mmol) of 1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]nonane-dihydrochloride in a mixture of 10 ml of acetonitrile and 5 ml of dimethylformamide. The mixture is evaporated, the residue is stirred with 30 ml of water, and the precipitate is filtered off with suction and dried at 80°C in vacuo.
Yield: 400 mg (34 % of theory of 1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-7-(1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid,
Melting point: 213-214°C (with decomposition).

B. 0.4 g of the betaine from Step A is dissolved in 5 ml of half-concentrated hydrochloric acid at room temperature, the solution is concentrated and the residue is stirred with about 3 ml of ethanol. The precipitate is filtered off with suction and dried at 80°C/12 mbar.
Yield: 290 mg (66 % of theory) of 1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-7-(1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid hydrochloride,
Melting point: 305-308°C (with decomposition),
$[\alpha]_D^{23}$: -79° (c = 0.52, H_2O)

Example 22



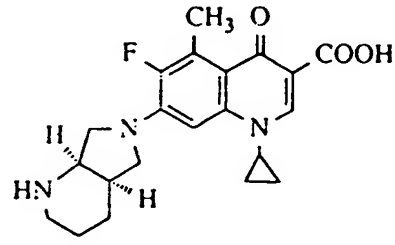
0.56 g (2 mmol) of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylate are heated at 120°C for 2 hours with 0.38 g (3 mmol) of [S,S]-2,8-diazabicyclo[4.3.0]nonane and 0.45 g (4 mmol) of 1,4-diazabicyclo[2.2.2]octane in 3.5 ml of dimethyl sulphoxide. After cooling, the solvent is removed in a high vacuum. The residue is taken up with acetonitrile. The solid is separated off, washed with acetonitrile and dried at 60 to 80°C.

Yield: 0.5 g (65 % of theory) of 1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylate

Melting point: 217-219°C (with decomposition),

$[\alpha]_D$: -119° (c = 0.5, DMF)

Example 23

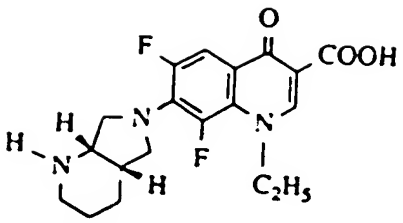


3 hours with 680 mg (5.4 mmol) of [S,S]-2,8-diazabicyclo[4.3.0]nonane in the presence of 560 mg (5 mmol) of 1,4-diazabicyclo[2.2.2]octane in 20 ml of acetonitrile. The suspension is filtered off with suction, washed with water and dried. 0.35 g of product is obtained. By concentrating the mother liquors, stirring the residue with water, isolating the undissolved product and purifing by chromatography (silica gel, eluent: dichloromethane/methanol/17 % strength aqueous ammonia), a further 0.7 g of product is isolated.
Total yield: 1.05 g (4[illegible] % of theory),
Melting point: 184-185°C (with decomposition)
$[\alpha]_D^{23}$: +6.8° (c = 0.46, $CHCl_3$).

B. 7-([S,S]-2,8-Diazabicyclo[4.3.0]non-8-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride

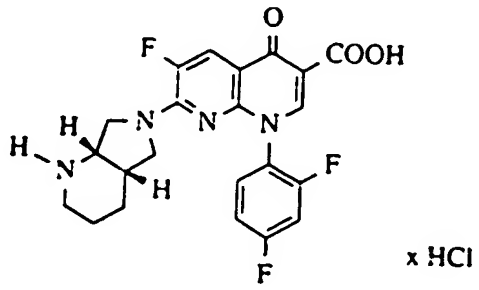
0.8 g (1.7 mmol) of the product from Step A are heated under reflux for 4 hours in a mixture of 10 ml of acetic acid and 8 ml of half-diluted hydrochloric acid. The mixture is concentrated, the residue is stirred with a little water, and the precipitate is filtered off with suction, washed with ice-cold ethanol and dried.
Yield: 0.67 g (83 % of theory),
Melting point: 324-326°C (with decomposition),
$[\alpha]_D^{25}$: +10.8° (c = 0.37, DMF).

Example 20



The reaction is carried out analogously to Example 1A using 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid and 1-ethyl-7-([S,S]-2,8-diazabicyclo[4.3.0]-non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of melting point 236-239°C (with decomposition) is obtained (recrystallised from glycol monomethyl ether);
$[\alpha]_D^{23}$: -186.3° (c = 0.3, $CHCl_3$).

Example 21



x HCl

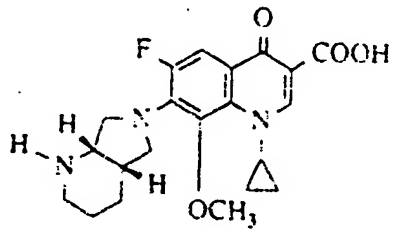
A. Ethyl 7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate

1.9 g (5 mmol) of ethyl 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate are stirred at 10°C for

methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxacine-6-carboxylic acid,
Melting point: 265-268°C (with decomposition),
$[\alpha]_D$: -232,2° (c = 0.58, $CHCl_3$)

3S-10-([S,S]-2,8-Diazabicyclo[4.3.0]non-8-yl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxacine-6-carboxylic acid is also obtained analogously.

Example 19



1-Cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid is reacted analogously to Example 1 and the reaction product is purified by chromatography (silica gel, eluent: methylene chloride/methanol/17 % strength aqueous ammonia = 30:8:1).

1-Cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid of melting point 203-208°C (with decomposition) is obtained.
$[\alpha]_D^{23}$: -193° (c = 0.4, $CHCl_3$).

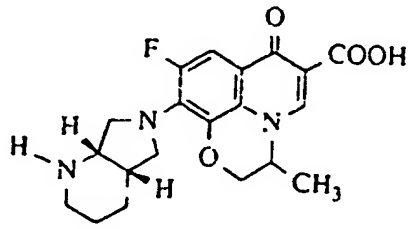
1.52 g (5 mmol) of ethyl 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate are reacted with 550 mg (5 mmol) of 1,4-diazabicyclo[2.2.2]octane and 760 mg (6 mmol) of (+)-[S,S]-2,8-diazabicyclo-[4.3.0]nonane in 30 ml of acetonitrile for 2 hours at 50°C and for 2 hours at 60°C. After cooling, the suspension obtained is filtered off with suction, and the precipitate is washed with water and dried at 90°C in vacuo.

Yield: 0.99 g (47.5 % of theory) of ethyl 1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate,

Melting point: 194-195°C (from acetonitrile),

$[\alpha]_D^{23}$: -188.9° (c = 0.51, $CHCl_3$).

Example 18



1.4 g (5 mmol) of 9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]-benzoxacine-6-carboxylic acid are reacted with 0.85 g (7.7 mmol) of 1,4-diazabicyclo[2.2.2]octane and 0.7 g (5.6 mmol) of (+)-[S,S]-2,8-diazabicyclo[4.3.0]nonane in 15 ml of acetonitrile/7.5 ml of dimethylformamide analogously to Example 1.

Yield: 1.24 g (64 % of theory) of 10-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-9-fluoro-2,3-dihydro-3-

390 mg (1 mmol) of 1-cyclopropyl-7-(2,8-diazabicyclo-[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate are dissolved in a solution of 40 mg of sodium hydroxide in 3 ml of water at room temperature in an ultrasonic bath and the solution is treated with ice-cooling with a solution of 160 mg (1.1 mmol) of R-(+)-α-methyl-benzyl isocyanate. The deposited precipitate is filtered off with suction, washed with dioxane and dried at 100°C in a high vacuum.

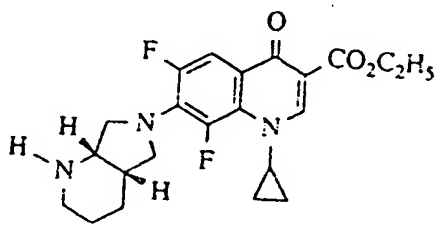
Yield: 530 mg (99 % of theory) of 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(2-[1R-phenyl-ethyl-amino-carbonyl]-2,8-diazabicyclo[4.3.0]non-8-yl)-3-quinoline-carboxylate,

Melting point: 208-210°C (with decomposition),

$[\alpha]_D^{25}$: -23.2° (c = 0.5, DMF).

The reaction product can be separated into the diastereomers by chromatography and the carbamoyl radical removed again by acidic hydrolysis, the compounds of Examples 1 and 7 being obtained.

Example 17

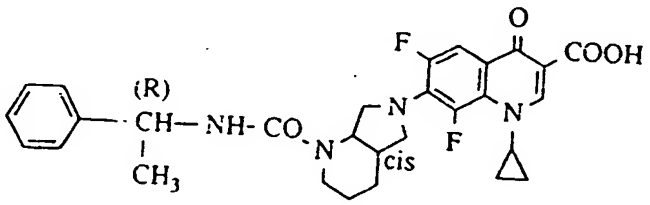


reacted overnight in the ultrasonic bath at 40-50°C. The suspension obtained is concentrated, and the residue is treated with water and extracted with methylene chloride. After drying with sodium sulphate, the solution is concentrated and the residue is purified by chromatography (silica gel, eluent: methylene chloride/methanol 95:5).
Yield: 950 mg (38 % of theory),
Melting point: 72-83°C (with decomposition).

C. 2S-Methyl-1-butyl 1-cyclopropyl-7-(2,8-diazabicyclo-[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate trifluoroacetate

570 mg (1 mmol) of the product of Step B are dissolved in 3 ml of trifluoroacetic acid at room temperature and the solution is concentrated at 60°C/12 mbar. The viscous oil obtained is stirred with 5 ml of ether, a solid product being obtained. This is filtered off with suction, washed with ether and dried at 80°C in a high vacuum.
Yield: 450 mg (78 % of theory),
Melting point: 214-216°C (with decomposition),
$[\alpha]_D^{25}$: +2.8° (c = 0.5, DMF).

Example 16



7.8 g (20 mmol) of 1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are dissolved in a mixture of 60 ml of dioxane/water (2:1) and 20 ml of 1 N sodium hydroxide solution and the mixture is treated with ice-cooling and stirring with 5.24 g (24 mmol) of di-tert-butyl pyro-carbonate. The mixture is stirred at room temperature for 1 hour and allowed to stand overnight. The deposited precipitate is filtered off with suction, washed with 250 ml of water and dried overnight at 50°C in a recirculating air drying oven.
Yield: 9.34 g (95.5 % of theory),
Melting point: 216-219°C (with decomposition).

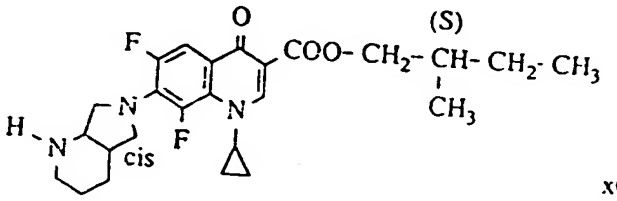
B. 2S-Methyl-1-butyl 7-(2-tert-butoxycarbonyl-2,8-diazabicyclo[4.3.0]non-8-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate

2.15 g (4.4 mmol) of the product from Step A are suspended in 60 ml of tetrahydrofuran/water (1:1) at room temperature and 1.65 g (5 mmol) of cesium carbonate are added. The mixture is allowed to react at about 40°C in an ultrasonic bath for 20 minutes, about 40 ml of the solvent are distilled off at 40°C/12 mbar) and the solution which remains is lyophilised, the slightly soluble crude caesium salt being obtained. 3.3 g of this crude salt are dissolved in 40 ml of dimethylformamide and treated with 1.4 g of S(+)-1-bromo-2-methyl-butane and

B. 5-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid is obtained analogously using the product from Example 13C,
Melting point: 212-214°C (with decompcsition),
$[\alpha]_D^{25}$: -260° (c = 0.5, DMP).

C. 5-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid is obtained analogously using the product from Example 13C,
Melting point: 213-215°C (with decomposition),
$[\alpha]_D^{25}$: +261° (c = 0.5, DMP).
Mass spectrum: m/e 406 (M^+,95 %), 346, 249, 98, 41, 28 (100 %).

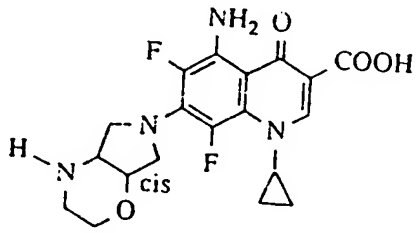
Example 15



A. 7-(2-tert-Butoxycarbonyl-2,8-diazabicyclo[4.3.0]non-8-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

C. 1-Cyclopropyl-5,6,8-trifluoro-1,4-dihydro-7-(1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid,
Melting point: 236-237°C (with decomposition).
$[\alpha]_D^{24}$: +282° (c = 0.5, DMF).

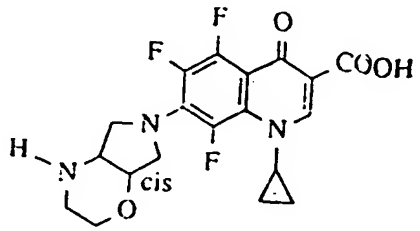
Example 14



A. 4.1 g (10 mmol) of the product from Example 13A are treated with 5 ml of liquid ammonia in 40 ml of pyridine and heated at 130°C for 10 hours in an autoclave. After cooling, the precipitate is filtered off with suction, washed with water and dried at 100°C in a recirculating air drying oven. The crude product (2 g) is purified by recrystallisation from glycol monomethyl ether: yellow crystallisate.
Yield: 1.3 g (31 % of theory) of 5-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(cis-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid,
Melting point: 233-240°C (with decomposition).

C. 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid hydrochloride,
Melting point: 300°C (decomposition)
$[\alpha]_D^{23}$: -99° (c = 0.5, H_2O).

Example 13



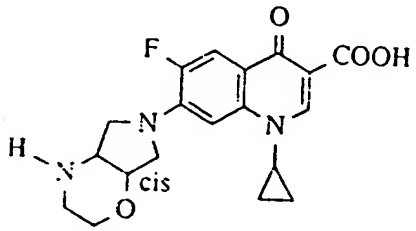
Analogously to Example 10A, the following are obtained using 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid:

A. 1-Cyclopropyl-5,6,8-trifluoro-1,4-dihydro-7-(cis-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid,
Melting point: 210-216°C (with decomposition).

B. 1-Cyclopropyl-5,6,8-trifluoro-1,4-dihydro-7-(1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid,
Melting point: 234-237°C (with decomposition).
$[\alpha]_D^{24}$: -287° (c = 0.5, DMF).

F. 8-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid hydrochloride,
Melting point: 292-294°C (with decomposition).
$[\alpha]_D^{27}$: +193° (c = 0.5, H_2O).

Example 12



Analogously to Example 10A, the following are obtained using 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid:

A. 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(cis-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid,
Melting point: 246-249°C (with decomposition) (from glycol monomethyl ether).

B. 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid,
Melting point: 243-245°C (with decomposition)

A. 8-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(cis-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl-4-oxo-3-quinolinecarboxylic acid,
Melting point: 180-185°C (with decomposition).

B. 8-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(cis-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid hydrochloride,
Melting point: 227-232°C (with decomposition).

C. 8-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid,
Melting point: 186-188°C (with decomposition).
$[\alpha]_D^{26}$: -269° (c = 0.5, DMF).

D. 8-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid hydrochloride
Melting point: 278-280°C (with decomposition).
$[\alpha]_D^{24}$: -208° (c = 0.5, H_2O).

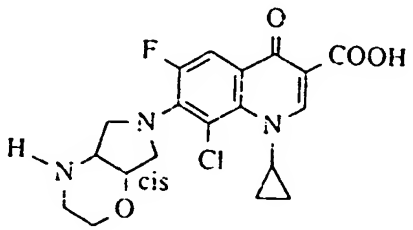
E. 8-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid
Melting point: 188-190°C (with decomposition).
$[\alpha]_D^{25}$: +270° (c = 0.5, DMF

E. Analogously to Example 10A, 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid of melting point 204-206°C (with decomposition) is obtained using 1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]nonane.
$[\alpha]_D^{25}$: +248° (c = 0.57, DMF).

F. Analagously to Example 10B, 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(1S,6R-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid hydrochloride of melting point 323°C (with decomposition) is obtained using betaine from Example 10E.

$[\alpha]_D^{26}$: +238° (c = 0.5, H_2O).

Example 11



Analogously to Example 10, the following are obtained using 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid:

B. 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(cis-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid hydrochloride:

1.6 g (4 mmol) of the product from Step A are dissolved in 120 ml of half-concentrated hydrochloric acid at 60°C, the solution is concentrated, the residue is stirred with ethanol and the precipitate is filtered off with suction and dried at 90°C in vacuo.

Yield: 1.57 g,

Melting point: 300-303°C (with decomposition),

Purity (HPLC): 97 % strength.

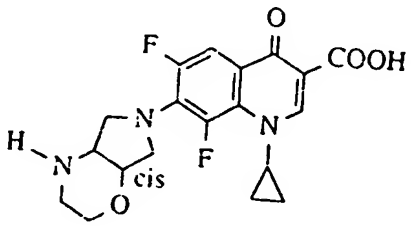
C. Analogously to Example 10A, 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid of melting point 204-206°C (with decomposition) is obtained using 1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]nonane.

D. Analogously to Example 10B, 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(1R,6S-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid hydrochloride of melting point 324-325°C (with decomposition) is obtained using the betaine from Example 10C.

$[\alpha]_D^{24}$: -241° (c = 0.59, H_2O).

B. 1-Cyclopropyl-7-([R,R]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,
Melting point: decomposition above 320°C,
$[\alpha]_D^{24}$: +92.5° (c = 0.53, H_2O).

Example 10



A. 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(cis-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid:

1.43 g (5 mmol) of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are heated under reflux for 1 hour with 0.74 g (5.4 mmol) of 93 % strength cis-2-oxa-5,8-diazabicyclo[4.3.0]nonane in the presence of 0.67 g (6 mmol) of 1,4-diazabicyclo[2.2.2]octane in a mixture of 15 ml of acetonitrile/75 ml of dimethylformamide. The suspension is concentrated, the residue is stirred with water, and the precipitate is filtered off with suction and dried in vacuo at 80°C.

Yield: 1.67 g (85.4 % of theory),
Melting point: 210-212°C (with decomposition).

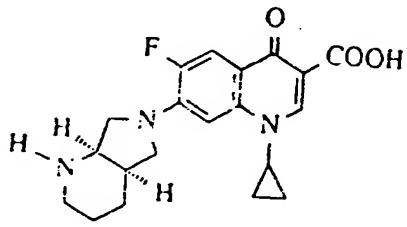
Melting point: 192-195°C (with decomposition).

B. 8-Chloro-1-cyclopropyl-7-([R,R]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-quinolinecarboxylic acid hydrochloride,
Melting point: 323-324°C (with decomposition).
Purity (HPLC): 99.9 % strength,
$[\alpha]_D^{24}$: +164.5° (c = 0.53, H_2O).

$C_{20}H_{21}ClFN_3O_3.HCl$ (442.3)

Calculated:	C 54.3	H 5.0	N 9.5	Cl 16.0
Found:	C 54.2	H 5.0	N 9.5	Cl 16.1

Example 9



Analogously to Example 1, the following are obtained from 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid and (-)-[R,R]-2,8-diazabicyclo-[4.3.0]nonane:

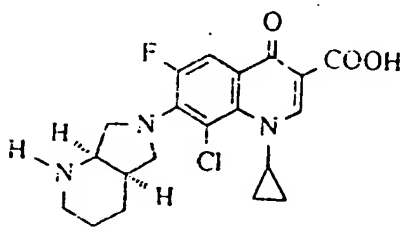
A. 1-Cyclopropyl-7-([R,R]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid,
Melting point: 254-258°C (with decomposition).

Analogously to Example 1, the following are obtained using (-)-[R,R]-2,8-diazabicyclo[4.3.0]nonane:

A. 1-Cyclopropyl-7-([R,R]-2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid
Melting point: 247-249°C (with decomposition).

B. 1-Cyclopropyl-7-([R,R]-2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride,
Melting point: 322-326°C (with decomposition),
Purity (HPLC): 99.4 % strength, ee: 98.6 %,
$[\alpha]_D^{24}$: +250° (c = 0.5, H_2O).

Example 8



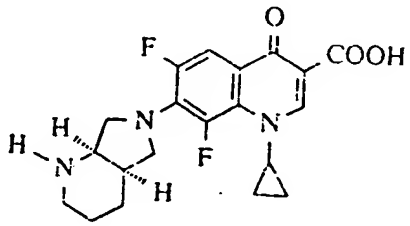
Analogously to Example 2, the following are obtained using (-)-[R,R]-2,8-diazabicyclo[4.3.0]nonane:

A. 8-Chloro-1-cyclopropyl-7-([R,R]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-quinolinecarboxylic acid,

1.4 g (5 mmol) of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid are stirred at room temperature for 1 hour with 1.3 g (10.3 mmol) of (+)-[S,S]-2,8-diazabicyclo[4.3.0]nonane with exclusion of water in 15 ml of acetonitrile. After standing overnight, the precipitate is filtered off with suction, washed with acetonitrile and chromatographed on silica gel for purification (eluent: methylene chloride/-methanol/17 % strength aqueous ammonia 30:8:1; R_f value: 0.4). The 1-cyclopropyl-7-([S,S]-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid obtained is dissolved in 15 ml of half-concentrated hydrochloric acid, the solution is evaporated and the residue is stirred with ethanol. The precipitate is filtered off with suction, washed with ethanol and dried at 120°C/12 mbar.

Yield: 960 mg (47 % of theory) of 1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride
Melting point: 345-346°C (with decomposition),
$[\alpha]_D^{30}$: +5.4° (c = 0.5, H_2O).

Example 7



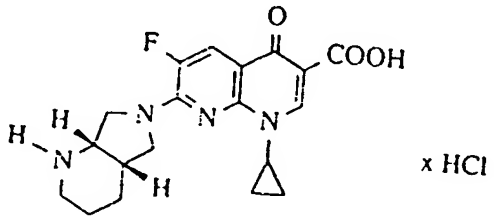
mixture is then cooled, the autoclave is let down, the mixture is concentrated and the residue is treated with acetonitrile in an ultrasonic bath. The undissolved precipitate is filtered off with suction, the residue is dissolved in about 150 ml of water in the presence of heat, the solution is filtered and the hydrochloride is precipitated using 10 ml of half-concentrated hydrochloric acid, filtered off with suction and dried at 100°C in a recirculating air drying oven. The product obtained is suspended in 100 ml of glycol monomethyl ether at 110-115°C and brought into solution by addition of 38 ml of half-concentrated hydrochloric acid. The solution is filtered hot through a glass frit, cooled and the cooled yellow crystallisate is filtered off with suction, washed with ethanol and dried at 120°C/12 mbar.

Yield: 2.5 g (44 % of theory) of 5-amino-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride,

Melting point: > 335°C (with decomposition; dark colouring already below 335°C),

$[\alpha]_D^{28}$: -280.8° (c = 0.53, H_2O).

Example 6

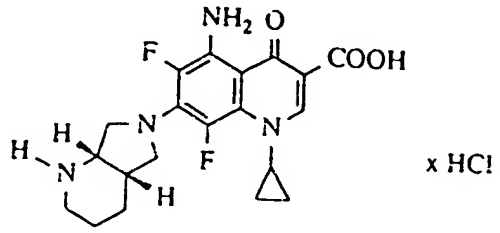


Yield: 6.7 g (82.3 % of theory) of 1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-5,6,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,
Melting point: 257-259°C (with decomposition); after recrystallisation from glycol monomethyl ether:
Melting point: 260-265°C (with decomposition).

B. 1.5 g (3.7 mmol) of the product from Step A are introduced into 6 ml of 1 N hydrochloric acid. After a short time, the hydrochloride deposits, and is filtered off with suction, washed twice with 5 ml of ethanol each time and dried at 100°C/12 mbar.

Yield: 1.4 g (85.7 % of theory) of 1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-5,6,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride,
Melting point: > 310°C (with decomposition),
$[\alpha]_D^{26}$: -272° (c = 0.5, H_2O).

Example 5



x HCl

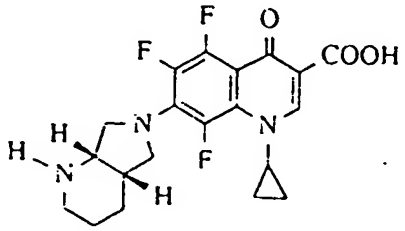
5.2 g (13 mmol) of the product from Example 4A are treated with 15 ml of liquid ammonia in 80 ml of pyridine in an autoclave and heated at 130°C for 12 hours. The

A. 1-Cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid
Melting point: 256-258°C (with decomposition).

B. 1-Cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-5-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride,

Melting point: > 320°C (with decomposition),
$[\alpha]_D^{26}$: -90.6° (c = 0.48, H_2O).

Example 4



A. 6 g (20 mmol) of 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are heated under reflux for 1 hour with 2.7 g (21.4 mmol) of (+)-[S,S]-2,8-diazabicyclo[4.3.0]nonane in 40 ml of acetonitrile/20 ml of N-methylpyrrolidone in the presence of 2.2 g (20 mmol) of 1,4-diazabicyclo[2.2.2]octane. The suspension obtained is cooled, and the precipitate is filtered off with suction, washed with acetonitrile and dried at 100°C/12 mbar.

quinoline carboxylic acid sulphate

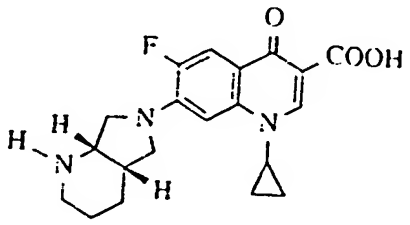
8-chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid acetate

8-chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid lactate

8-chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid citrate

8-chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid embonate

Example 3



Analogously to Example 1, the following are obtained with 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid:

concentrated in vacuo and the residue is stirred with about 300 ml of abs. ethanol. The suspension is cooled in ice, the precipitate is filtered off with suction, washed with ethanol and dried first at room temperature and then at 100°C in vacuo.

Yield: 13.4 g (93.8 % of theory);
Melting point: 328-330°C (with decomposition);
R_f value (silica gel, methylene chloride/methanol/17 % strength aqueous NH_3 = 30:8:1): 0.4;
Purity (HPLC): 99.9 % strength,
$[\alpha]_D^{24}$: -164.4° (c = 0.45, H_2O),

$C_{20}H_{21}ClFN_3O_3.HCl$ (442.3)

Calculated:	C 54.3	H 5.0	N 9.5	Cl 16.0
Found:	C 54.3	H 5.0	N 9.5	Cl 16.0

C. The following salts, for example, can also be prepared analogously:

8-chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid methanesulphonate

8-chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid toluenesulphonate

8-chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-

presence of 99 g (0.88 mol) of 1,4-diazabicyclo[2.2.2]-octane (DABCO) (internal temperature: 90.5°C). The yellow solution is cooled and treated with seed crystals (obtained from a 5 ml sample which was concentrated; residue stirred with acetronitrile). The mixture is stirred for 2 hours at about 3°C, and the deposited precipitate from both batches is rapidly filtered off with suction, washed with acetronitrile and introduced into 1.5 l of ice-water. The initially thin, well-stirrable suspension after about 10 minutes becomes a poorly stirrable mass, which is diluted with a further 150 ml of water. The precipitate is filtered off with suction, washed with water and dried at 80°C in a recirculating air drying oven.

Yield: 402 g (82.7 % of theory), faintly yellow product;
Melting point: 193-196°C (with decomposition),
R_f value (silica gel; methylene chloride/methanol/17 % strength aqueous NH_3 = 30:8:1): 0.4.

B. 8-Chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride

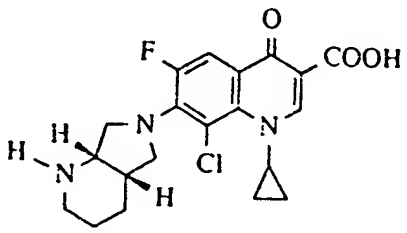
13.1 g (32 mmol) of 8-chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are suspended in 50 ml of water and brought into solution by addition of 50 ml of half-concentrated hydrochloric acid. The mixture is filtered through a glass frit, the filtrate is

Melting point: 324-325°C (with decomposition),
TLC (silica gel, dichloromethane/methanol/17 % strength aqueous ammonia = 30:8:1): homogeneous, R_f value: 0.3,
$[\alpha]_D^{25}$: -256° (c = 0.5, H_2O),
Purity (HPLC): 99.4 % strength,

$C_{20}H_{21}F_2N_3O_3.HCl$ (425.5)

Calculated:	C 56.4	H 5.2	N 9.9	Cl 8.3
Found:	C 56.3	H 5.4	N 9.8	Cl 8.3

Example 2



A. 8-Chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

2 batches of the following size are run in parallel and worked up together:

180 g (0.6 mol) of 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are heated under reflux for 1 hour with 84 g (0.67 mol) of (+)-[S,S]-2,8-diazabicyclo[4.3.0]nonane in a mixture of 1.8 l of acetonitrile/900 ml of dimethylformamide in the

oven.

Yield: 163.4 g (84 % of theory),
Melting point: 249-251°C (with decomposition)

B. (-)-1-Cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride

6.0 g (15.4 mmol) of 1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are dissolved in 40 ml of half-concentrated hydrochloric acid at 60°C and the solution of the hydrochloride is filtered. The filtrate is concentrated to one half, cooled in ice and treated with 40 ml of ethanol. The yellow crystallisate is filtered off with suction, washed with ethanol and dried at 60°C in a high vacuum, where the colour lightens. 5.51 g (84 % of theory) of the hydrochloride are obtained, which is already very pure.

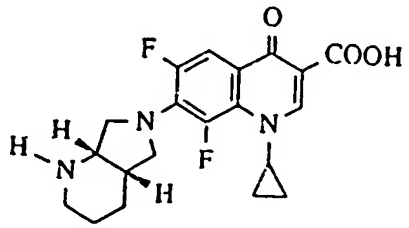
For further purification, it is dissolved in 50 ml of water in the presence of heat. The yellow solution is treated with 5 ml of half-concentrated hydrochloric acid and cooled in ice, and the deposited crystallisate is filtered off with suction, washed well with ethanol and dried first at room temperature and then under a high vacuum at 100°C.

Yield: 4.64 g (70.8 % of theory),

NMR ^1H (DMSO): 8.73 s (1H at C-2), 4,16 m (1H, cyclopropyl), 1,2 m (4H, cyclopropyl) [ppm].
Mass spectrum: m/e 361 (M^+-H_2O), 317 ($M-CO_2$), 41 (100 %, C_3H_5).

Preparation of the final compounds

Example 1



A. 1-Cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

141.5 g (0.5 mol) of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are heated under reflux for 1 hour with 69.25 g (0.55 mol) of (+)-[S,S]-2,8-diazabicyclo[4.3.0]nonane (ee 99.5 %, GC 99.8 % strength) in a mixture of 1500 ml of acetonitrile and 750 ml of dimethylformamide in the presence of 55 g (0.5 mol) of 1,4-diazabicyclo-[2.2.2]octane. The suspension is cooled, and the precipitate is filtered off with suction, washed with water and then additionally stirred with 1 l of water (pH 7). The product is filtered off with suction and dried at 60°C in a recirculating air

28 g (68 mmol) of ethyl 2-(2-bromo-3,4,5,6-tetrafluoro-benzoyl)-3-cyclopropylaminoacrylate are heated under reflux for 6 hours with 6.9 g (164 mmol) of sodium fluoride in 88 ml of DMF. The mixture is poured into water after cooling, and the deposited precipitate (red) is filtered off with suction, washed with plenty of water and dried at 80°C in a recirculating air oven.
Crude yield: 27.3 g,
Melting point: 150-175°C;
after recrystallisation from glycol monomethyl ether:
Melting point: 187-191°C.

7) 5-Bromo-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

26.7 g (68 mmol) of crude ethyl 5-bromo-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate are introduced into a mixture of 165 ml of acetic acid, 110 ml of water and 18 ml of concentrated sulphuric acid and heated under reflux for 2 hours. The cooled reaction mixture is poured into ice-water, and the deposited precipitate is filtered off with suction, washed with plenty of water and dried in a recirculating air oven at 80°C.
Yield: 19.7 g (80 % of theory),
Melting point: 208-210°C (with decomposition);
after recrystallisation from glycol monomethyl ether:
Melting point: 212-214°C (with decomposition);

4) Ethyl 2-(2-bromo-3,4,5,6-tetrafluoro-benzoyl)-3-ethoxy-acrylate

45 g of crude ethyl (2-bromo-3,4,5,6-tetrafluoro-benzoyl)-acetate are introduced into 32.2 g (0.31 mol) of acetic anhydride and 28.4 g (0.19 mol) of triethyl orthoformate and the mixture is heated under reflux for 2 hours. Excess reagent is first stripped off in vacuo, then under a high vacuum (bath up to 120-130°C) and the crude product is reacted to the next step.
Crude yield: 50.7 g

5) Ethyl 2-(2-bromo-3,4,5,6-tetrafluoro-benzoyl)-3-cyclopropylamino-acrylate

50.7 g of crude product from Step 4) are treated dropwise with 8.6 g (0.15 mol) of cyclopropylamine in 90 ml of ethanol with ice-cooling, the mixture is stirred at room temperature, allowed to stand overnight and again well cooled, and the crystallisate is filtered off with suction, washed with cold ethanol and dried.
Yield: 29 g (42 % over 4 steps),
Melting point: 103-105°C (from ethanol).

6) Ethyl 5-bromo-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate

introduced into 150 ml of anhydrous acetonitrile (dried over zeolite) and 26.9 g (0.167 mol) of diethyl malonate are allowed to drop in with cooling. The mixture is cooled to 0°C, 46 ml (33.7 g = 0.33 mol) of triethylamine are added dropwise and the mixture is stirred for 30 minutes. 48.9 g (0.168 mol) of 2-bromo-3,4,5,6-tetrafluoro-benzoyl chloride are then added dropwise, and the mixture is stirred for a further 1 hour at 0°C and brought to room temperature overnight. It is treated with 100 ml of 5 N hydrochloric acid and extracted three times with methylene chloride, and the extracts are dried with Na_2SO_4 and concentrated in vacuo.

Crude yield: 62.7 g.

3) Ethyl (2-bromo-3,4,5,6-tetrafluoro-benzoyl)-acetate

60 g of crude diethyl (2-bromo-3,4,5,6-tetrafluoro-benzoyl)-malonate are introduced into 150 ml of water and treated with 0.6 g of 4-toluenesulphonic acid, and the mixture is heated under reflux for 6 hours. It is extracted with methylene chloride, and the extract is washed with water, dried with Na_2SO_4 and concentrated.

Crude yield: 46 g,

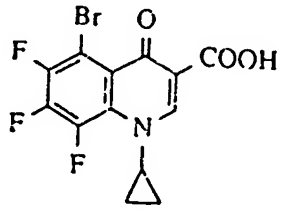
Boiling point (sample distillation in a bulb tube): 150-160°C(oven)/3 mbar;

Mass spectrum: %, 342 (M^+), 297 ($M^+-OC_2H_5$), 263 (M^+-Br), 257, 255 ($M^+-CH_2CO_2C_2H_5$), 235 (263-28).

Derivatisation with Mosher reagent and gas chromatographic analysis shows only one detectable enantiomer (ee ≥ 99.5 %).

Example M

5-Bromo-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid



1) 2-Bromo-3,4,5,6-tetrafluoro-benzoyl chloride

365 g (1.33 mol) of 2-bromo-3,4,5,6-tetrafluoro-benzoic acid [Tetrahedron 23, 4719 (1967)] are introduced into 2 l of thionyl chloride and the mixture is heated under reflux for 11 hours until the evolution of gas stops. Excess thionyl chloride is stripped off in vacuo and the residue is distilled.

Yield: 330 g (85 % of theory),
Boiling point: 81-85°C/3-5 mbar.

2) Diethyl (2-bromo-3,4,5,6-tetrafluoro-benzoyl)-malonate

15.9 g (0.167 mol) of magnesium chloride are

n-butanol.
Yield: 15 g (39.6 % of theory of optically pure material.
Melting point: 188°C,
Rotation : $[\alpha]_D^{28} = +103.7°$ (c = 1, $CHCl_3$).

2) 1R,6S-8-Tosyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane

13 g (33.6 mmol) of 1R,6S-5-(1R-phenylethyl)-8-tosyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane are hydrogenated at 100°C and 100 bar on 2.5 g of palladium/active carbon (10 % Pd) in 200 ml of ethanol. The catalyst is filtered off with suction, the filtrate is concentrated and the residue is recrystallised from 30 ml of toluene.
Yield: 7.5 g (79 % of theory),
Melting point: 160-161°C,
Rotation: $[\alpha]_D^{23} = +17.5°$ (c = 1.21, $CHCl_3$).

3) 1R,6S-2-Oxa-5,8-diazabicyclo[4.3.0]nonane dihydrobromide

7 g (24.8 mmol) of 1R,6S-8-tosyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane are dissolved in 25 ml of 33 % strength hydrogen bromide solution in glacial acetic acid, 5 g of phenol are added and the mixture is stirred overnight at room temperature. It is diluted with diisopropyl ether, and the crystallised salt is filtered off with suction and dried in air.
Yield: 5.5 g.

The reaction is carried out analogously to Example J2) using 1R,6S-5-benzyl-2-oxa-5,8-diazabicyclo-[4.3.0]nonane:

Yield: 93.3 % of theory (1.58 molar batch)

Boiling point: 63 - 65°C/0.03 mbar

Rotation: $[\alpha]_D^{23} = -8.4°$ (undiluted).

ee value: ≥ 99.5 % (by derivatisation with Mosher reagent).

1R,6R- or 1S,6S-2-Oxa-5,8-diazabicyclo[4.3.0]nonane can be obtained analogously.

Example L

1R,6S-2-Oxa-5,8-diazabicyclo[4.3.0]nonane dihydrobromide

1) 1R,6S-5-(1R-Phenylethyl)-8-tosyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane

101.8 g (0.196 mol) of trans-3-brom-1-tosyl-4-(2-tosyloxyethoxy)-pyrrolidine and 72 g (0.584 mol) of R-(+)-1-phenylethylamine in 900 ml of xylene are heated under reflux overnight. The cooled solution is washed with 2N sodium hydroxide solution and dried over potassium carbonate, the drying agent is removed and the solvent is concentrated. On cooling, crystals are deposited from the residue which are filtered off with suction and recrystallised from a mixture of 750 ml of petroleum ether and 200 ml of

Yield: 4.6 g (66.5 % of theory)
Melting point: 233-235°C.

2) 1S,6R-2-Oxa-5,8-diazabicyclo[4.3.0]nonane

59 g (0.27 mol) of 1S,6R-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane are hydrogenated at 120°C and 120 bar on 5 g of palladium/active carbon (10 % Pd) in 500 ml of ethanol. The catalyst is filtered off with suction, the filtrate is concentrated and the residue is distilled.
Yield: 32.9 g (95 % of theory)
Boiling point: 65°C/0.03 mbar
Rotation : $[\alpha]_D^{20} = +8.2°$ (undiluted).
ee value: ≥ 99.5 % (by derivatisation with Mosher reagent).

Example K

1) 1R,6S-2-Oxa-5,8-diazabicyclo[4.3.0]nonane dihydrochloride

The reaction is carried out analogously to Example J1) using 1R,6S-5-benzyl-2-oxa-5,8-diazabicyclo-[4.3.0]nonane:
Yield: 77 % of theory (23.8 mmolar batch)
Melting point: 230-232°C.

2) 1R,6S-2-Oxa-5,8-diazabicyclo[4.3.0]nonane

The reaction is carried out analogously to Example H4) using 3R,4R-1-tert-butoxy-carbonyl-3-tosyloxy-4-(2-tosyloxyethoxy)-pyrrolidine:
Yield: 40 % of theory (0./1 molar batch).

5) 1R,6S-5-Benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane

The reaction is carried out analogously to Example H5) using tert-butyl 1R,6S-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane-8-carboxylate:
Yield: 63 % of theory (40 mmolar batch)
Boiling point: 120°C/0.06 mbar
The product is 95 % strength by gas chromatography
$[\alpha]_D^{23}$ = +58.5° (undiluted).

Example J

1) 1S,6R-2-Oxa-5,8-diazabicyclo[4.3.0]nonane dihydrochloride

7.5 g (34.4 mmol) of 1S,6R-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane are hydrogenated at 100°C and 100 bar on 1 g of palladium/active carbon (10 % Pd) in 200 ml of ethanol with the addition of 7 ml of concentrated hydrochloric acid. The catalyst is filtered off with suction and washed several times with water. The aqueous filtrate is concentrated, whereupon the residue crystallises. The crystals are thoroughly saturated with ethanol, filtered off with suction and dried in air.

Example I

1) tert-Butyl 3R,4R-4-allyloxy-3-hydroxypyrrolidine-1-carboxylate

The reaction is carried out analogously to Example H1) using tert-butyl R,R-3,4-dihydroxypyrrolidine-1-carboxylate:
Boiling point: 145°C/0.1 mbar
$[\alpha]_D^{23}$ = +9.5° (c = 1.0, methanol).
The product is 95 % strength by gas chromatography.

2) tert-Butyl 3R,4R-3-hydroxy-4-(2-hydroxyethoxy)-pyrrolidine-1-carboxylate

The reaction is carried out analogously to Example H2) using tert-butyl 3R,4R-4-allyloxy-3-hydroxy-pyrrolidine-1-carboxylate:
Yield: 99 % of theory (0.175 molar batch)
$[\alpha]_D^{20}$ = +16.5° (c = 0.94, methanol).

3) 3R,4R-1-tert-Butoxycarbonyl-3-tosyloxy-4-(2-tosyloxyethoxy)-pyrrolidine

The reaction is carried out analogously to Example H3) using tert-butyl 3R,4R-3-hydroxy-4-(2-hydroxyethoxy)-pyrrolidine-1-carboxylate
Yield: quantitative (0.11 molar batch).

4) tert-Butyl 1R,6S-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane-8-carboxylate

4) tert-Butyl 1S,6R-5-benzyl-2-oxa-5,8-diazabicyclo-[4.3.0]nonane-8-carboxylate

87 g (156 mmol) of 3S,4S-1-tert-butoxycarbonyl-3-tosyloxy-4-(2-tosyloxyethoxy)-pyrrolidine are heated under reflux overnight with 58 g (0.54 mol) of benzylamine in 1 l of xylene. The mixture is cooled, precipitated salts of benzylamine are filtered off with suction and the residue is concentrated.
Yield: 43 g (58 % of theory).
The product is 67 % strength by gas chromatography.

5) 1S,6R-5-Benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane

43 g (90 mmol) of tert-butyl 1S,6R-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane-8-carboxylate are heated under reflux in 35 ml of concentrated hydrochloric acid and 35 ml of water until the evolution of carbon dioxide is complete. The mixture is rendered alkaline with potassium carbonate and extracted with chloroform, the organic solutions are dried over $MgSO_4$ and concentrated, and the residue is distilled twice through a 20 cm Vigreux column.
Yield: 11.1 g (55 % of theory)
Boiling point: 108 - 115°C/0.07 mbar
$[\alpha]_D^{26} = -58.3°$ (undiluted).

20 g of potassium carbonate and extracted five times with 100 ml of methylene chloride each time. The organic solutions are dried over magnesium sulphate and concentrated.

Yield: 65.8 g (100 % of theory)

The product is 91 % strength by gas chromatography. $[\alpha]_D^{20} = -15.2^\circ$ (c = 0.97, methanol).

3) 3S,4S-1-tert-Butoxycarbonyl-3-tosyloxy-4-(2-tosyloxyethoxy)-pyrrolidine

2.7 g (10 mmol, 91 % strength) of tert-butyl 3S,4S-3-hydroxy-4-(2-hydroxyethoxy)-pyrrolidine-1-carboxylate are initially introduced into 30 ml of methylene chloride, 6 ml of 45 % strength sodium hydroxide solution and 0.1 g of benzyltriethylammonium chloride are added and a solution of 2.86 g (20 mmol) of tosyl chloride in 10 ml of methylene chloride are then added dropwise with cooling. The mixture is then stirred for a further hour at room temperature and poured into 20 ml of water, the organic phase is separated off and the aqueous phase is extracted with methylene chloride. The organic phases are dried over magnesium sulphate and concentrated.

Yield: 5 g (90 % of theory).

The product is homogenous by thin layer chromatography.

tert-butyl methyl ether (200 ml). 9 g of starting material (44 mmol) crystallised out overnight. The ether solution is concentrated and distilled.

Yield: 83 g (80 % of theory relative to recovered starting material and diallyl ether)
Boiling point: 149°C/0.7 mbar to 159°C/0.9 mbar.

The distillate contains 5 % of the starting material and 4 % of diallyl ether.
The pentane extract yielded 17 g of a mixture of 15 % desired product and 84 % of diallyl ether.
$[\alpha]_D^{23} = -10.5°$ (c = 1, methanol).

2) tert-Butyl 3S,4S-3-hydroxy-4-(2-hydroxyethoxy)-pyrrolidine-1-carboxylate

64 g (0.24 mol, 91 % strength) of tert-butyl 3S,4S-4-allyloxy-3-hydroxypyrrolidine-1-carboxylate are dissolved in 250 ml of methanol and cooled to 0°C, and ozone is passed through the solution until a washing bottle containing potassium iodide solution and connected in series indicates the emergence of ozone and thus complete reaction. Residues of ozone are carried out by means of a stream of nitrogen, then the resulting ozonide is reduced at 0°C using 18 g of sodium borohydride, which is added in 1 g portions. The mixture is then stirred overnight at room temperature and concentrated, the residue is diluted with water, and the mixture is treated with

$[\alpha]_D^{23}$ = +61.2° (undiluted).

The separation of enantiomers described for cis-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane can also be carried out analogously with trans-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane to give R,R- and S,S-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane.

Example H

1) tert-Butyl 3S,4S-4-allyloxy-3-hydroxypyrrolidine-1-carboxylate

16.5 g (0.55 mol) of 80 % strength NaH are initially introduced into 500 ml of absolute dioxane and a solution of 107.5 g (0.53 mol) of tert-butyl S,S-3,4-dihydroxypyrrolidine-1-carboxylate (DE-A-3,403,194) dissolved hot in absolute dioxane is added dropwise at 60°C. The mixture is stirred at 60°C for 1 hour and 64 g (0.53 mol) of allyl bromide are then added dropwise. The mixture is then stirred at 60°C for three hours. It is concentrated and the residue is dissolved in 200 ml of water and 600 ml of methanol. The solution is extracted three times with 200 ml of pentane each time, the methanol is stripped off on a rotary evaporator, the residue is diluted with 200 ml of water and the mixture is extracted with methylene chloride. The methylene chloride solution is dried over $MgSO_4$ and concentrated, and the residue is dissolved in

product is then dried in air.

Yield: 145.5 g of 1S,6R-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane L-tartrate (79 % of theory)

Melting point: 174.5 to 176.5°C

ee > 97 % (after derivatisation with 1-phenyl-ethyl isocyanate and HPLC analysis)

$[\alpha]_D^{23}$ = -24.0° (c = 1, methanol).

Liberation of the enantiomerically pure bases:

144 g (0.39 mol) of 1S,6R-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane tartrate are dissolved in 250 ml of water and 175 ml (1.05 mol) of 6 N sodium hydroxide solution are added. The deposited oil is taken up in 500 ml of toluene, the organic phase is separated off and the aqueous phase is extracted a further 3 times with 250 ml of toluene in each case. The combined organic phases are dried over sodium carbonate, filtered and concentrated on a rotary evaporator. The residue is distilled through a 20 cm Vigreux column under a high vacuum.

Yield: 81.6 g (96 % of theory) of 1S,6R-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane

Boiling point: 120 to 139°C/0.04 to 0.07 mbar

Purity: 100 % determined by gas chromatography

Density: δ = 1.113 g/ml

$[\alpha]_D^{23}$ = -60.9° (undiluted).

Distillation residue: 0.12 g

In the same manner, 76.0 g (93 % of theory) of 1R,6S-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane are obtained from 139.2 g (0.376 mol) of 1R,6S-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane tartrate.

$[\alpha]_D^{23}$ = +24.0° (c = 1, methanol).

156.9 g of the 1st crystallisate are recrystallised from 1,500 ml of methanol.
Yield: 140.0 g (89 % recovered)
Melting point: 176 to 177°C
$[\alpha]_D^{23}$ = +25.2° (c = 1, methanol).

The methanolic mother liquor from the 1st crystallisation is concentrated on a rotary evaporator. The syrupy residue (236 g) is dissolved in 500 ml of water, adjusted to pH 12 to 13 with 250 ml of 6N sodium hydroxide solution, extracted 3 times with 350 ml of toluene each time, and the extracts are dried over sodium carbonate and concentrated in vacuo. The residue, 113.1 g of a brown oil which, according to gas chromatographic investigation, contains 97 % of cis-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane, is employed without purification for the preparation of the 1S,6R-enantiomer.

113.1 g (0.518 mol) of crude concentrated 1S,6R-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane are dissolved in 155 ml of methanol and added dropwise to a boiling solution of 77.8 g (0.518 mol) of L-(+)-tartaric acid in 363 ml of methanol. A crystal magma is gradually formed during the dropwise addition. The mixture is stirred at 60°C for 1 hour and then slowly cooled to 0°C in the course of 2 hours. The crystals are filtered off with suction and washed with a 2:1 mixture of ethanol and methanol cooled to 0°C and then 3 times with ethanol. The

Yield: 17.1 g (77 % of theory),
Melting point: 244-250°C.

Example G

Separation of enantiomers of cis-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane

150.1 g (1 mol) of D-(-)-tartaric acid are initially introduced into 700 ml of methanol at 60 to 65°C and 218.3 g (1 mol) of cis-5-benzyl-2-oxa-5,8-diazabicyclo-[4.3.0]nonane are added dropwise as a solution in 300 ml of methanol. The mixture is then slowly allowed to cool to about 49°C until the solution becomes cloudy, and is seeded with crystals of 1R,6S-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane D-tartrate obtained in a prior experiment, stirred for 30 minutes at this temperature for seed crystal formation and then slowly cooled down to 0 to 3°C. After filtering off with suction, the solid is washed with a mixture of 200 ml of ethanol and 100 ml of methanol cooled to 0°C and then 3 times with 300 ml of ethanol in each case and the product is then dried in air.

Yield: 160.3 g of 1R,6S-5-benzyl-2-oxa-5,8-diazabicyclo-[4.3.0]nonane tartrate (87 % of theory)
Melting point: 174.5 to 176.5°C
ee > 97 % (after derivatisation with 1-phenyl-ethyl isocyanate and HPLC analysis).

Crude yield: 91.2 g.

4) cis-5-Benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane

91 g (0.265 mol) of cis-8-benzoyl-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane are heated under reflux overnight with 200 ml of concentrated hydrochloric acid and 140 ml of water. After cooling, the benzoic acid is filtered off with suction, the filtrate is concentrated to half the volume, the solution is rendered alkaline with potassium carbonte and extracted with chloroform, the extract is dried over potassium carbonate and concentrated, and the residue is distilled.

Yield: 30.7 g (48.8 % of theory),
Boiling point: 134-142°C/0.6 mbar,
Purity by GC: 92 %.

5) cis-2-Oxa-5,8-diazabicyclo[4.3.0]nonane dihydrochloride

26 g (0.11 mol, 92 % strength) of cis-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane in 180 ml of ethanol and 19 ml of concentrated hydrochloric acid are hydrogenated in 3 g of palladium/active carbon (10 % Pd) at 100°C and 100 bar. The catalyst is filtered off with suction, the filtrate is concentrated and the separated crystals are dried in a dessicator over phosphorus pentoxide.

2) trans-1-Benzoyl-3-bromo-4-(2-tosyloxyethoxy)-pyrrolidine

92 g (0.239 mol) of trans-1-benzoyl-3-bromo-4-(2-hydroxyethoxy)-pyrrolidine, 32 g (0.316 mol) of triethylamine and 1 g of 4-dimethylaminopyridine are dissolved in 750 ml of toluene and 60 g (0.31 mol) of tosyl chloride in 450 ml of toluene are added dropwise. The mixture is stirred at room temperature for two days, water is added, and the aqueous phase is separated off and extracted with toluene. The toluene solutions are washed with 10 % strength hydrochloric acid, dried over magnesium sulphate and concentrated, the residue is dissolved in ethyl acetate and the solution is filtered through silica gel. The filtrate is concentrated.

Yield: 125 g (91 % of theory).

The thin layer chromatogram shows a homogeneous compound.

3) cis-8-Benzoyl-5-benzyl-2-oxa-5,8-diazabicyclo[4.3.0]nonane

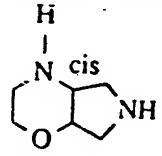
124 g (0.265 mol) of trans-1-benzoyl-3-bromo-4-(2-tosyloxyethoxy)-pyrrolidine are heated under reflux overnight with 86 g (0.8 mol) of benzylamine in 1.5 l of xylene, the salts of benzylamine are filtered off with suction and the filtrate is concentrated.

Purity: 95 % strength,

^{1}H-NMR ($CDCl_3$, 200 MHz): 1.4-1.7 (m, 3H); 1.82 and 1.83 (2d, 3H); 1.9-2.05 (m, 1H); 2.28 (broad s, 1H); 2.54-2.86 (m, 3H); 3.77 (d, 1H); 5.39 (q. 1H); 7.24-7.48 ppm (m, 5H).

Example F

cis-2-Oxa-5,8-diazabicyclo[4.3.0]nonane



1) trans-1-Benzoyl-3-bromo-4-(2-hydroxyethoxy)-pyrrolidine

95 g (0.55 mol) of 1-benzoyl-3-pyrroline are dissolved in 380 g of ethylene glycol and 101 g (0.57 mol) of N-bromosuccinimide are added in 5 g portions in the course of 2 hours. The mixture is then stirred overnight at room temperature, poured into water and extracted with methylene chloride, and the solution is dried over magnesium sulphate and concentrated. The residue (188 g) was chromatographed on silica gel using ethyl acetate.

Yield: 136.5 g (78 % of theory),
Purity by GC: 99 %.

of S-(-)-1-phenyl-ethylamine are added dropwise, whereupon the temperature rises to 33°C. The mixture is stirred for a further 1 hour and then concentrated on a rotary evaporator, and residual solvent is removed at 40°C/0.1 mbar. The residue is taken up in 245 g (2.4 mol) of acetic anhydride, and the solution is treated with 4.9 g (0.06 mol) of anhydrous sodium acetate and stirred at 100°C for 1 hour. After cooling, the mixture is poured onto 1 l of ice-water while stirring well, and the precipitate is filtered off with suction, washed with cold water and hexane and dried in air.
The crude product (114 g, Melting point: 112-114°C) is recrystallised from 285 ml of methanol.

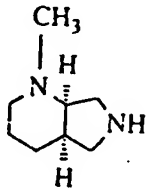
Yield: 96.3 g (76 %),
Melting point: 115-117°C,
$[\alpha]_D^{22} = -46.9°$ (c = 2, ethanol).

2) cis-7,9-Dioxo-8-([1S]-1-phenyl-ethyl)-2,8-diazabicyclo[4.3.0]nonane

79.7 g (0.316 mol) of N-([1S]-1-phenylethyl)-pyridine-2,3-dicarboximide are hydrogenated over 10 g of palladium on active carbon (5 % strength) at 90°C/100 bar in 600 ml of tetrahydrofuran. The catalyst is filtered off after completion of the absorption of hydrogen and the filtrate is completely concentrated. 83.7 g of a viscose residue are obtained.

Example D

[R,R]-2-Methyl-2,8-diazabicyclo[4.3.0]nonane

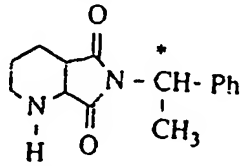


The compound is prepared by the working instructions described in Example C, starting from 43.2 g (0.2 mol) of [R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane.

Yield: 4.9 g of [R,R]-2-methyl-2,8-diazabicyclo[4.3.0]-nonane.
Boiling point: 30-33°C/0.12 mbar.

Example E

cis-7,9-Dioxo-8-([1S]-1-phenyl-ethyl)-2,8-diazabicyclo[4.3.0]nonane



1) N-([1S]-1-Phenyl-ethyl)pyridine-2,3-dicarboximide

74.5 g (0.5 mol) of pyridine-2,3-dicarboxylic anhydride are initially introduced at 20°C in solution in 500 ml of dioxane and 60.5 g (0.5 mol)

2 g of palladium on active carbon (5 %) at 20°C and 20 bar for 10 hours. The catalyst is then filtered off with suction, the filtrate is rendered alkaline with potassium carbonate and the product is extracted with tert-butyl methyl ether. After drying over sodium sulphate, the mixture is concentrated and the residue is distilled in vacuo.

Yield: 14.8 g,
Boiling point: 114-124°C/0.14 mbar.

2) [S,S]-2-Methyl-2,8-diazabicyclo[4.3.0]nonane

12.9 g (56 mmol) of [S,S]-8-benzyl-2-methyl-2,8-diazabicyclo[4.3.0]nonane are hydrogenated over 1.1 g of palladium on active carbon (5 %) at 90°C and 90 bar in 90 ml of methanol. The mixture is then filtered, the filtrate is concentrated on a rotary evaporator and the residue is distilled in vacuo.

Yield: 5.5 g of enantiomerically pure [S,S]-2-methyl-2,8-diazabicyclo[4.3.0]nonane (detection by derivatisation with Mosher's reagent),
Boiling point: 78-81°C/14 mbar.

It was not possible to determine any racemisation during the gas chromatographic determination of the enantiomer purity using menthyl chloroformate.

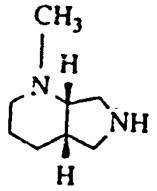
2) [R,R]-2,8-diazabicyclo[4.3.0]nonane

19.4 g (0.09 mol) of [R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane are hydrogenated according to the procedure of Example A, 2.

Yield: 9.61 g (85 % of [R,R]-2,8-diazabicyclo-[4.3.0]nonane,
Boiling point: 45-58°C/0.08 mbar,
$[\alpha]_D^{23}$ = +2.30° (undiluted).

Example C

[S,S]-2-Methyl-2,8-diazabicyclo[4.3.0]nonane



1) [S,S]-8-Benzyl-2-methyl-2,8-diazabicyclo[4.3.0]-nonane

43.2 g (0.2 mmol) of [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane are treated with 20 ml of 37 % formaldehyde solution, 40 ml of water and 24 g of acetic acid and the mixture is hydrogenated over

concentrated.

Yield 2.2 g (99 % of theory) of [1R,6S]-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane
Melting point: 60-61°C,
$[\alpha]_D^{23}$ = +21.8° (c = 5, ethanol).

An enantiomer excess of 93.8 % ee was determined by gas chromatography after derivatisation with menthyl chloroformate.

b) Reduction of [1R,6S]-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane to [R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane

In a heated flask, 0.34 g (9 mmol) of lithium aluminium hydride is introduced under N_2 in 18 ml of anhydrous tetrahydrofuran and 0.73 g (3 mmol) of [1R,6S]-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]-nonane is added dropwise as a solution in 3 ml of anhydrous tetrahydrofuran. The mixture is then boiled for 16 hours with reflux condensation. Working up is carried out by dropwise edition of 0.34 ml of water in 10 ml of tetrahydrofuran, 0.34 ml of 10 % strength sodium hydroxide solution and 1.02 ml of water. The precipitate is filtered off with suction and washed with tetrahydrofuran, and the filtrate is concentrated. 0.7 g of crude [R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane remains (GC purity: 99 %).

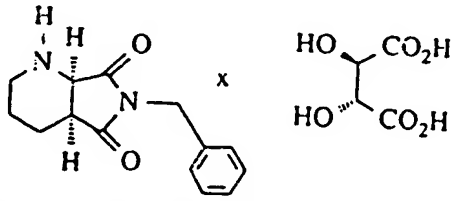
recrystallising twice from a mixture of ethanol and glycol monomethyl ether:
$[\alpha]_D^{23}$ = +58.6° (c = 0.5, 1N HCl).

^{1}H-NMR (DMSO): 7.22-7.35 (2m, 2H, aryl-H); 4.55 (s, 2H, benzyl-CH_2); 4.28 (s, 2H, tartaric acid-CH); 3.91 (d, 1H, 1-CH); 2.97 (dd, 1H, 6-CH); 2.53-2.66 (m, 2H, 3-cH_2); 1.78 and 1.68 (2m, 2H, 5-CH_2); 1.42 and 1.28 ppm (2m, 2H, 4-CH_2).

$C_{18}H_{22}N_2O_8$(394)

Calculated:	C 54.4	H 5.6	N 7.1	O 32.5
Found:	C 54.7	H 5.8	N 7.1	O 32.4

The determination of the absolute configuration was carried out by means of an X-ray structural analysis:



3.6 g (9.1 mmol) of the diastereomerically pure tartrate obtained in this manner are dissolved in water to liberate the base and treated with saturated sodium hydrogen carbonate solution until a pH of 7 to 8 is obtained. The aqueous solution is extracted four times with 20 ml of methylene chloride each time. The combined methylene chloride phases are dried over magnesium sulphate and

$[\alpha]_D^{24} = -17.5°$ (undiluted).

Method II

a) Separation of enantiomers of cis-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane to give [1R,6S]-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane

24.1 g (98.8 mmol) of cis-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane are heated to reflux with stirring in a mixture of 410 ml of ethanol and 25 ml of acetonitrile in a three-necked flask. 14.8 g (98.8 mmol) of L-(+)-tartaric acid are then added at once. After all the tartaric acid has completely dissolved, the heating is first turned off, but the flask is left in the oil bath. When the system has cooled until the solution no longer boils, the stirrer is turned off. Crystallisation and addition of seed crystals takes place at a temperature of 50°C. After standing overnight and cooling to room temperature, the precipitated crystals are filtered off with suction and washed with a little ethanol/petroleum ether (1:1) and dried at 80°C for 2 hours.

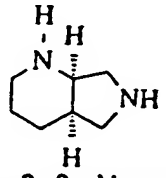
Yield: 9.8 g (50 % of theory) of [1R,6S]-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane L-tartrate, $[\alpha]_D^{23} = +47.7°$ (c = 0.5, 1N HCl).

The compound can be further purified by

chloroformate).

Example B

[R,R]-2,8-Diazabicyclo[4.3.0]nonane



1) [R,R]-8-Benzyl-2,8-diazabicyclo[4.3.0]nonane

Method I:

The crystals of [R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]-nonane obtained according to Example A, Method II (49.2 g) are washed with dimethylformamide and methoxyethanol and recrystallised from 300 ml of methoxyethanol. 45.6 g of enantiomerically pure [R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane L-tartrate are obtained (enantiomer purity determined by gas chromatography after derivatisation with menthyl chloroformate).

Melting point: 121-124°C,
$[\alpha]_D^{23}$ = +22.3° (c = 1, H_2O).

The salt (44.5 g) is converted into the free base as described in Example A, Method Ib. 20.2 g of [R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane are obtained.

Boiling point: 107-111°C/0.04 mbar,

initially introduced in solution in 50 ml of dimethylformamide at 80°C and 10.82 g (50 mmol) of cis-8-benzyl-2,8-diazabicyclo[4.3.0]nonane are added dropwise as a solution in 15 ml of dimethylformamide. The mixture is seeded with [R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]-nonane L-tartrate and stirred for one hour at about 72°C to complete seed crystal formation. This is then slowly cooled to 15°C, and the crystals are filtered off with suction and washed twice with 13 ml of dimethylformamide in each case. The combined filtrates are heated to 80°C and treated with a further 3.75 g (25 mmol) of L-(+)-tartaric acid. The mixture is additionally heated to 119°C until a clear solution is formed, and again slowly cooled to room temperature with seeding with [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]-nonane L-tartrate. The crystals are filtered off with suction, washed successively with dimethyl-formamide, 2-methoxy-ethanol and ethanol and dried in air.

Yield: 9.59 g

Melting point: 188 to 192°C.

The crystals are recrystallised from 95 ml of 80 % strength ethanol. 8.00 g of [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane L-tartratetrihydrate (76 % of theory) are obtained which melts at 112 to 118°C with foaming, then resolidifies and melts again at 199 to 201°C.

$[\alpha]_D^{23} = 4.5°$ (c = 1, water).

ee: 98.0 % (determined by gas chromatography after derivatisation with menthyl

The procedure is analogous to Example B (Method II, b), [1S,6R]-8-benzyl-7,9-dioxo-2,8-diazabicyclo-[4.3.0]nonane being, however, employed as the starting material.

The crude product obtained after working up proved to be [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane on derivatisation with menthyl chloroformate. Racemisation was thus observed during the reduction.

2) [S,S]-2,8-Diazabicyclo[4.3.0]nonane

28.4 g (0.131 mol) of [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane are hydrogenated at 90°C and 90 bar in the course of 5 hours over 5.8 g of palladium on active carbon (5%) in 190 ml of methanol. The catalyst is then filtered off with suction and washed with methanol, and the filtrate is concentrated on a rotary evaporator. The residue is distilled without fractionation.

Yield: 15.0 g (90.5 % of theory) of [S,S]-2,8-diazabicyclo[4.3.0]nonane,
Boiling point: 44-59°C/0.18 mbar,
$[\alpha]_D^{22} = -2.29°$ (undiluted),
ee > 99 % (determined by gas chromatography after derivatisation with Mosher's reagent).

Method V:

3.75 g (25 mmol) of L-(+)-tartaric acid are

These 14.4 g (59 mmol) are crystallised from 120 ml of ethanol analogously to Example B (Method II/a) using 8.6 g (57 mmol) of D-(-)-tartaric acid.

Yield: 8.9 g (77 % of theory) of [1S,6R]-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane D-tartrate.
$[\alpha]_D^{23}$ = -46.2° (c = 0.5, 1N HCl);
after recrystallisation from an ethanol/glycol monomethyl ether mixture a further purification is carried out:
$[\alpha]_D^{23}$ = -59.3° (c = 0.5, 1N HCl).

5.0 g (12.7 mmol) of the diastereomerically pure tartrate obtained in this manner were converted, as described in Example B, Method II/a, into the free amine:

Yield: 3.0 g (96 % of theory) of [1S,6R]-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane,
Melting point: 60-61°C,
$[\alpha]_D^{23}$ = -22.2° (c = 5, ethanol).

An enantiomer excess of 96.6 % ee was determined by gas chromatography after derivatisation with menthyl chloroformate.

b) Reduction of [1S,6R]-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane to [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane.

(liberation of the base) to give enantiomerically pure [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane.

Method IV:

a) Separation of enantiomers of cis-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane to give [1S,6R]-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane.

The procedure is analogous to Example B (Method II/a), using D-(-)-tartaric acid as the chiral auxiliary reagent, or the procedure is as follows:

Mother liquor and washing liquor from [1R,6S]-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane L-tartrate (from Example B, Method II/a) are concentrated together, the residue is taken up in water and the solution is extracted three times with toluene. The toluene phases are discarded. The aqueous phase is treated with saturated sodium hydrogen carbonate solution until a pH of 7 to 8 is obtained, then extracted four times with methylene chloride. The combined methylene chloride phases are dried over magnesium sulphate and concentrated.

Yield: 14.4 g (60 % of theory of the originally employed racemic cis-8-benzyl-7,9-dioxo-2,8-diazabicyclo[4.3.0]nonane).
$[\alpha]_D^{23} = -4.5^\circ$ (c = 5, ethanol).

according to Method I to give diastereomerically pure [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonan D-tartrate. Recrystallisation in this case is not necessary.

Method III:

73.6 g (0.34 mol) of cis-8-benzyl-2,8-diazabicyclo-[4.3.0]nonane are added dropwise at 80 to 90°C as a solution in 111 ml of dimethylformamide to a solution of 102.9 g (0.685 mol) of L(+)-tartaric acid in 343 ml of dimethylformamide. The mixture is seeded with [R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane L-tartrate and slowly cooled to an internal temperature of 18°C. The crystals are filtered off with suction, and the filtrate is seeded with [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]-nonane L-tartrate and stirred until it has crystallised completely. (After concentration and liberation of the base as described in Method I, [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane D-tartrate can be obtained from the mother liquor by purification with D-tartaric acid). The product is then filtered off with suction, washed with dimethylformamide and isopropanol and dried in air. The crystals are recrystallised from 88 % strength ethanol. 52 g of [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]-nonane L-tartrate trihydrate are obtained.

Melting point: 201-204°C,
$[\alpha]_D^{23} = +5.2°$ (c = 1, H_2O).

The salt can be processed as described in Method I

residue is then distilled in vacuo.

Yield: 18.5 g of [S,S]-8-Benzyl-2,8-diazabicyclo-[4.3.0]nonane,
Boiling point: 107-109°C/0.1 mbar,
$[\alpha]_D^{24}$ = 17.3° (undiluted).

Method II:

75.0 g (0.5 mol) of L-(+)-tartaric acid are dissolved in 250 ml of dimethylformamide at 80°C and 54.1 g (0.25 mol) of cis-8-benzyl-2,3-diazabicyclo[4.3.0]nonane are added dropwise as a solution in 75 ml of dimethylformamide. The mixture is slowly cooled to 20°C and the crystal suspension is stirred for 1 hour. The crystals ([R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane L-tartrate) are filtered off with suction and the filtrate is concentrated on a rotary evaporator. The residue is dissolved in 500 ml of water and worked up as described in Method I using 63 g of 45 % strength sodium hydroxide solution.

Yield: 25.2 g of [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]-nonane;
the product contains 3.6 % of the R,R-enantiomer (determined by gas chromatography after derivatisation with menthyl chloroformate).

The compound can be reacted with D-(-)-tartaric acid

3.0 g (20 mmol) of D-(-)-tartaric acid are dissolved in 10 ml of dimethylformamide by heating to 80°C and the solution is treated with a solution of 2.16 g (10 mmol) of cis-8-benzyl-2,8-diazabicyclo[4.3.0]-nonane in 3 ml of dimethylformamide. The mixture is stirred at 0°C for 1 hour, and the product is filtered off with suction and washed with dimethylformamide and methoxyethanol.

Yield: 1.93 g,
Melting point: 146-151°C,
$[\alpha]_D^{23}$ = -19.3° (c = 1, H_2O).

Diastereomerically pure [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane D-tartrate is obtained by a single recrystallisation from methoxyethanol.

$[\alpha]_D^{23}$ = -22.7° (c = 1, H_2O).
Melting point: 148-154°C.

b) Liberation of the base:

40 g of [S,S[-8-benzyl-2,8-diazabicyclo[4.3.0]nonane D-tartrate are dissolved in 250 ml of water and treated with 32 g of 45 % strength sodium hydroxide solution. The precipitated oil is taken up in 150 ml of tert-butyl methyl ether, the aqueous phase is extracted again with 150 ml of tert-butyl methyl ether and the combined organic phases are concentrated after drying over sodium sulphate. The

Table

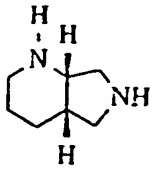
Species	Strain	Compound A	Compound B	Compound C
Bacteroides fragilis	ES 25	0.25	1	8
	DSM 2151	0.25	0.5	4
Clostridium perfringens	1024027	0.125	0.5	0.5
Bact. thetaiotaomicron	DSM 2079	0.5	2	8

(MIC values in µg/ml; agar dilution test in the multipoint inoculator (Denley); isosensitest agar).

Preparation of the precursors

Example A

[S,S]-2,8-Diazabicyclo[4.3.0]nonane



1) [S,S]-8-Benzyl-2,8-diazabicyclo[4.3.0]nonane

Method I:

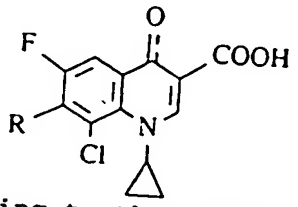
a) Separation of the diastereomeric salts:

The tabl below confirms the surprising advantages of the compounds according to the invention compared with ciprofloxacin in the Staphylococcus aureus-infected mouse model:

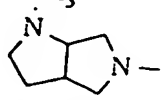
Table: Activity in Staph. aureus infection in the mouse (mg/kg)

Substance	p.o.	s.c.
Ciprofloxacin	80	80
Example 27	10	2.5
Example 29A	5	5
Example 31	10	10
Example 33	10	5
Example 35	2.5	2.5

The compounds according to the invention, compared to known structurally similar compounds, show an improved antibacterial action, in particular with anaerobic microorganisms.



Component according to the invention as in Example 2B: A

R = 

, disclosed in EP-A-0,350,733: B

Ciprofloxacin C

to the amount to b employed, but also to the rat of destruction. It was possible to observe results of this type with gram-positive and gram-negative bacteria, in particular with Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus faecalis and Escherichia coli.

The compounds according to the invention also show surprising increases in activity against bacteria which are classified as less sensitive to comparable substances, in particular resistant Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Enterococcus faecalis.

The compounds according to the invention are particularly active against bacteria and bacteria-like microorganisms. They are therefore particularly highly suitable for the prophylaxis and chemotherapy of local and systemic infections in human and veterinary medicine which are caused by these pathogens.

The compounds are also suitable for controlling protozoonoses and helminthoses.

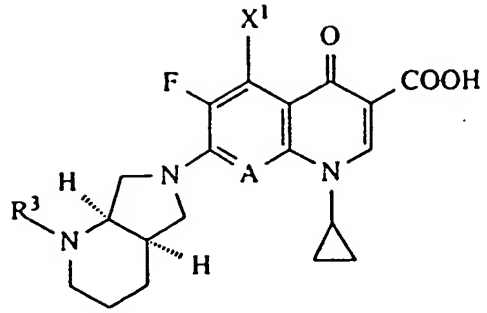
The compounds according to the invention can be used in various pharmaceutical preparations. Preferred pharmaceutical preparations which may be mentioned are tablets, coated tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays.

The compounds according to the invention have potent antibiotic activity and exhibit, together with low toxicity, a broad antibacterial spectrum against gram-positive and gram-negative microorganisms, in particular against enterobacteria; especially even against those which are resistant to various antibiotics, such as, for example, penicillins, cephalosporins, aminoglycosides, sulphonamides and tetracyclines.

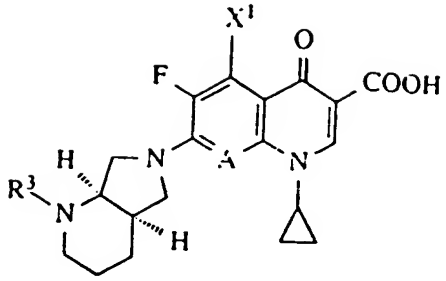
These useful properties make possible their use as chemotherapeutic active substances in medicine and also as substances for the preservation of inorganic and organic materials, in particular of organic materials of all types, for example polymers, lubricants, dyes, fibres, leather, paper and wood, of foodstuffs and of water.

The compounds according to the invention are active against a very broad spectrum of mircoorganisms. With their aid, gram-negative and gram-positive bacteria and bacteria-like microorganisms can be controlled and the diseases produced by these pathogens can be prevented, ameliorated and/or cured.

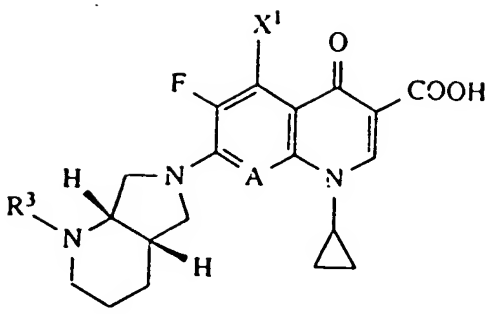
The compounds according to the invention are distinguished by increased activity on dormant and resistant microorganisms. In the case of dormant bacteria, e.g. bacteria which show no detectable growth, the compounds act at concentrations which are far below those of substances known hitherto. This relates not only



R^3	X^1	A
$C_2H_5O_2C$-CH=C-$CO_2C_2H_5$	H	C-H
$C_2H_5O_2C$-CH=CH-	H	C-H
CH_3O_2C-CH=CH-	F	C-F
$C_2H_5O_2C$-CH_2-CH_2-	F	C-F
$C_2H_5O_2C$-CH=CH-	NH_2	C-F
$C_2H_5O_2C$-CH=C-$CO_2C_2H_5$	NH_2	C-F
CH_3-CO-CH_2CH_2-	CH_3	C-H
$C_2H_5O_2C$-CH=CH-	CH_3	C-H
$C_2H_5O_2C$-CH=C-$CO_2C_2H_5$	CH_3	C-H
CH_3O_2C-CH=C-$CO_2C_2H_5$	CH_3	N
CH_3-CO-CH_2CH_2-	H	C-OCH_3
$C_2H_5O_2C$-CH=CH-	H	C-OCH_3
$C_2H_5O_2C$-CH=CH	H	N
NC-CH_2CH_2	H	N
CH_3-CO-CH_2CH_2	H	N

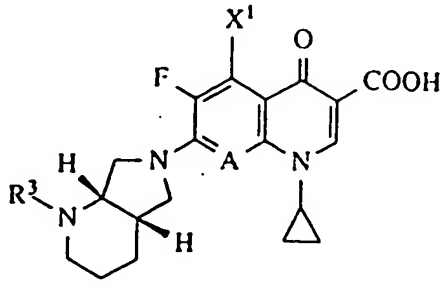


R^3	X^1	A
CH_3-CO-CH_2CH_2-	H	C-F
CH_3-CO-CH_2-	H	C-F
$C_2H_5O_2C$-CH_2CH_2-	H	C-F
NC-CH_2CH_2-	H	C-F
CH_3O_2C-CH=CH-	H	C-F
CH_3O_2C-CH=C-CO_2CH_3	H	C-F
$C_2H_5O_2C$-CH=C-$CO_2C_2H_5$	H	C-F
5-Methyl-2-oxo-1,3-dioxol-4-yl-methyl-	H	C-F
CH_3-CO-CH_2CH_2-	H	C-Cl
CH_3-CO-CH_2-	H	C-Cl
$C_2H_5O_2C$-CH_2CH_2-	H	C-Cl
NC-CH_2CH_2-	H	C-Cl
CH_3O_2C-CH=CH-	H	C-Cl
CH_3O_2C-CH=C-CO_2CH_3	H	C-Cl
$C_2H_5O_2C$-CH=C-$CO_2C_2H_5$	H	C-Cl
5-Methyl-2-oxo-1,3-dioxol-4-yl-methyl-	H	C-Cl



R^3	X^1	A
$C_2H_5O_2C$-CH=CH-	NH_2	C-F
CH_3-CO-CH_2CH_2-	H	N
$C_2H_5O_2C$-CH_2-CH_2-	H	N
NC-CH_2CH_2-	H	N
$C_2H_5O_2C$-CH=C-$CO_2C_2H_5$	H	N
CH_3O_2C-CH=CH-	H	N
CH_3-CO-CH_2CH_2-	CH_3	C-H
CH_3-CO-CH_2-	CH_3	C-H
$C_2H_5O_2C$-CH_2CH_2-	CH_3	C-H
$C_2H_5O_2C$-CH=C-$CO_2C_2H_5$	CH_3	C-H
CH_3O_2C-CH=C-CO_2CH_3	CH_3	C-H
$C_2H_5O_2C$-CH=CH-	CH_3	C-H
CH_3O_2C-CH=CH-	CH_3	C-F
$C_2H_5O_2C$-CH=C-$CO_2C_2H_5$	CH_3	N

following tables (optionally in the cis- or trans-form) can also be prepared by the processes described:



R^3	X^1	A
$C_2H_5O_2C\text{-}CH_2\text{-}CH_2\text{-}$	H	C-F
$CH_3O_2C\text{-}CH{=}CH\text{-}$	H	C-F
$NC\text{-}CH_2\text{-}CH_2\text{-}$	H	C-F
5-Methyl-2-oxo-1,3-dioxol-4-yl-methyl-	H	C-F
$CH_3\text{-}CO\text{-}CH_2\text{-}$	H	C-Cl
5-Methyl-2-oxo-1,3-dioxol-4-yl-methyl-	H	C-Cl
$CH_3\text{-}CO\text{-}CH_2\text{-}CH_2\text{-}$	H	C-H
$CH_3\text{-}CO\text{-}CH_2\text{-}$	H	C-H
$C_2H_5O_2C\text{-}CH_2\text{-}CH_2$	H	C-H
$C_2H_5O_2C\text{-}CH{=}C(CO_2C_2H_5)\text{-}$	H	C-H
$CH_3O_2C\text{-}CH{=}CH\text{-}$	H	C-H
$C_2H_5O_2C\text{-}CH{=}CH\text{-}$	F	C-F
$CH_3\text{-}CO\text{-}CH_2CH_2\text{-}$	NH_2	C-F
$C_2H_5O_2C\text{-}CH_2CH_2\text{-}$	NH_2	C-F
$CH_3O_2C\text{-}CH{=}C(CO_2CH_3)\text{-}$	NH_2	C-F
$C_2H_5O_2C\text{-}CH{=}C(CO_2C_2H_5)\text{-}$	NH_2	C-F

The preparation of the acid addition salts of the compounds according to the invention is carried out in a customary manner, for example by dissolving the betaine in aqueous acid and precipitating the salt with a water-miscible organic solvent such as methanol, ethanol, acetone or acetonitrile. Equivalent amounts of betaine and acid can also be heated in water or an alcohol such as glycol monomethyl ether and then evaporated to dryness or the precipitated salt filtered off with suction. Pharmaceutically utilisable salts are understood as meaning, for example, the salts of hydrochloric acid, sulphuric acid, acetic acid, glycolic acid, lactic acid, succinic acid, citric acid, tartaric acid, methanesulphonic acid, 4-toluenesulphonic acid, galacturonic acid, gluconic acid, embonic acid, glutamic acid or aspartic acid.

The alkali metal or alkaline earth metal salts of the carboxylic acids according to the invention are obtained, for example, by dissolving the betaine in excess alkali metal or alkaline earth metal hydroxide solution, filtering off undissolved betaine and evaporating the filtrate to dryness. Pharmaceutically suitable salts are sodium, potassium or calcium salts. By reacting an alkali metal or alkaline earth metal salt with a suitable silver salt such as silver nitrate, the corresponding silver salts are obtained.

Apart from the active substances mentioned in the examples, for example, the compounds listed in the

The reaction can be carried out at normal pressure, but also at elevated pressure. In general, it is carried out at pressures between about 1 and 100 bar, preferably between 1 and 10 bar.

When carrying out this process, 1 to 15 mol, preferably 1 to 6 mol, of the compound (III) are employed per mol of the compound (II).

The reaction of (II) with the Michael acceptors (IV) according to method B is preferably carried out in a diluent such as acetonitrile, dimethyl sulphoxide, N,N-dimethylformamide, an alcohol such as methanol, ethanol, propanol or isopropanol, or glycol monomethyl ether.

The reaction temperatures can be varied within a relatively wide range. In general, the reaction is carried out between about 20°C and about 150°C, preferably between 40°C and 100°C.

The reaction can be carried out at normal pressure, but also at elevated pressure. In general, the reaction is carried out at pressures between 1 and 100 bar, preferably between 1 and 10 bar.

When carrying out the process according to the invention, 1 to 5 mol, preferably 1 to 2 mol, of the compound (IV) are employed per mol of the compound (II).

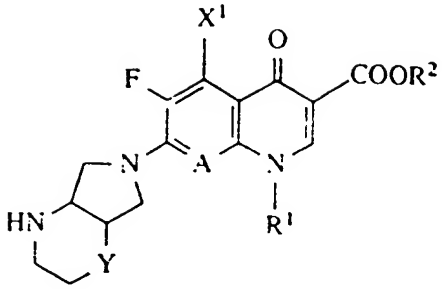
The starting compounds of the structures (III) and (IV) are known. Examples which may be mentioned are:

chloroacetone, 4-chloro-2-butanone, 5-chloro-2-pentanone, 1-bromo-2-butanone, phenacyl chloride, methyl acrylates, ethyl acrylates, acrylonitrile, methyl vinyl ketone, dimethyl acetylenedicarboxylate, diethyl acetylene-dicarboxylate, methyl propiolate and ethyl propiolate.

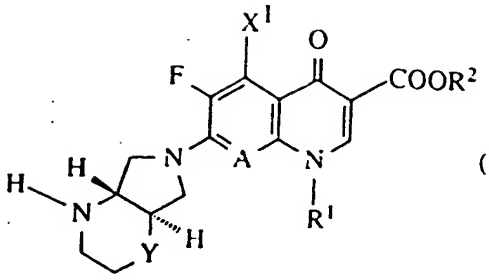
The reaction of (II) with (III) is preferably carried out in a diluent such as dimethyl sulphoxide, N,N-dimethyl-formamide, N-methylpyrrolidone, hexamethylphosphoramide, sulpholane, acetonitrile, water, an alcohol such as methanol, ethanol, n-propanol or isopropanol, glycol monomethyl ether or pyridine in the presence of an acid binder. Mixtures of these compounds can also be used.

Acid binders which can be used are all the customary inorganic and organic acid binders. These preferably include the alkali metal hydroxides, alkali metal carbonates, organic amines and amidines. Those which may be specifically mentioned as being particularly suitable are: triethylamine, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or excess amine (VI).

The reaction temperatures can be varied within a relatively wide range. In general the reaction is carried out between about 20 and 200°C, preferably between 60 and 130°C.

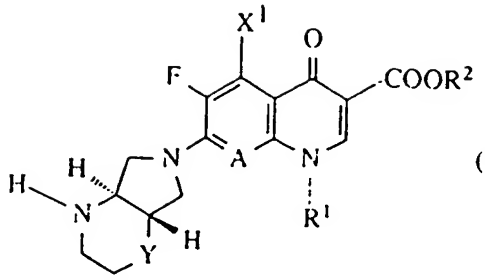


R^1	R^2	X^1	Y	A
2,4-Difluorophenyl	H	Cl	CH_2	C-F
2,4-Difluorophenyl	H	CH_3	CH_2	C-F
2,4-Difluorophenyl	H	H	CH_2	C-CH_3
2,4-Difluorophenyl	H	H	O	C-F
2,4-Difluorophenyl	H	H	O	C-Cl
4-Fluorophenyl	H	H	O	CH
2,4 Difluorophenyl	H	H	O	N
2,4-Difluorophenyl	H	H	O	C-OCH_3
2,4-Difluorophenyl	H	H	O	C-CH_3
2,4-Difluorophenyl	H	H	CH_2	C-F
2,4-Difluorophenyl	H	F	CH_2	C-F
2,4-Difluorophenyl	H	H	CH_2	C-Cl
2,4-Difluorophenyl	H	H	O	C-Cl
2,4-Difluorophenyl	H	H	CH_2	N
2,4-Difluorophenyl	H	H	O	N
2,4-Difluorophenyl	H	H	O	C-H
2,4-Difluorophenyl	C_2H_5	H	O	C-F



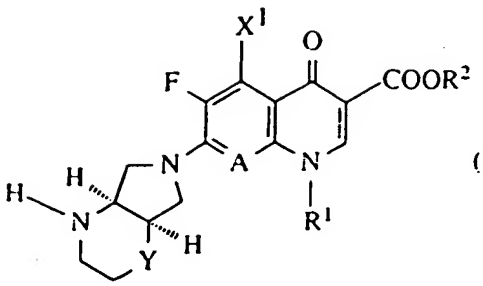
(II)

R^1	R^2	X^1	Y	A
Cyclopropyl	H	H	CH_2	C-H
Cyclopropyl	H	H	CH_2	C-F
Cyclopropyl	H	H	CH_2	C-Cl
Cyclopropyl	H	H	CH_2	C-OCH_3
Cyclopropyl	H	H	CH_2	C-CH_3
Cyclopropyl	H	H	CH_2	N
Cyclopropyl	H	Br	CH_2	C-F
Cyclopropyl	H	F	CH_2	C-F
Cyclopropyl	H	CH_3	CH_2	C-F
Cyclopropyl	H	NH_2	CH_2	C-F
Cyclopropyl	H	H	O	C-H
Cyclopropyl	H	H	O	C-F
Cyclopropyl	H	H	O	C-Cl
Cyclopropyl	H	H	O	C-OCH_3
Cyclopropyl	H	H	O	C-CH_3
Cyclopropyl	H	H	O	N
Cyclopropyl	H	Br	O	C-F
Cyclopropyl	H	F	O	C-F
Cyclopropyl	H	CH_3	O	C-F
Cyclopropyl	H	NH_2	O	C-F



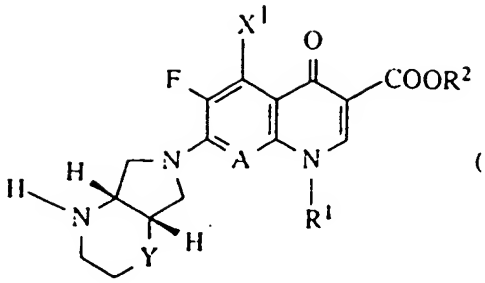
(II)

R^1	R^2	X^1	Y	A
Cyclopropyl	H	H	CH_2	C-H
Cyclopropyl	H	H	CH_2	C-F
Cyclopropyl	H	H	CH_2	C-Cl
Cyclopropyl	H	H	CH_2	C-OCH_3
Cyclopropyl	H	H	CH_2	C-CH_3
Cyclopropyl	H	H	CH_2	N
Cyclopropyl	H	Br	CH_2	C-F
Cyclopropyl	H	F	CH_2	C-F
Cyclopropyl	H	CH_3	CH_2	C-F
Cyclopropyl	H	NH_2	CH_2	C-F
Cyclopropyl	H	H	O	C-H
Cyclopropyl	H	H	O	C-F
Cyclopropyl	H	H	O	C-Cl
Cyclopropyl	H	H	O	C-OCH_3
Cyclopropyl	H	H	O	C-CH_3
Cyclopropyl	H	H	O	N
Cyclopropyl	H	Br	O	C-F
Cyclopropyl	H	F	O	C-F
Cyclopropyl	H	CH_3	O	C-F
Cyclopropyl	H	NH_2	O	C-F



(II)

R^1	R^2	X^1	Y	A
Cyclopropyl	CH_3	H	CH_2	C-H
Cyclopropyl	CH_2CH_2OH	H	CH_2	C-F
Cyclopropyl	CH_2CH_2OH	H	CH_2	C-Cl
Cyclopropyl	H	H	CH_2	C-OCH_3
Cyclopropyl	H	H	CH_2	C-CH_3
Cyclopropyl	H	H	CH_2	N
Cyclopropyl	H	Br	CH_2	C-F
Cyclopropyl	H	F	CH_2	C-F
Cyclopropyl	H	CH_3	CH_2	C-F
Cyclopropyl	H	NH_2	CH_2	C-F
Cyclopropyl	H	H	O	C-H
Cyclopropyl	CH_3	H	O	C-F
C_2H_5	H	H	O	C-Cl
Cyclopropyl	H	H	O	C-OCH_3
Cyclopropyl	H	H	O	C-CH_3
Cyclopropyl	H	H	O	N
Cyclopropyl	H	Br	O	C-F
Cyclopropyl	H	Cl	O	C-F
Cyclopropyl	H	CH_3	O	C-F
C_2H_5	H	NH_2	O	C-F



(II)

R^1	R^2	X^1	Y	A
Cyclopropyl	C_2H_5	H	CH_2	C-H
F-CH_2CH_2	H	H	CH_2	C-F
Cyclopropyl	C_2H_5	H	CH_2	C-Cl
Cyclopropyl	H	H	CH_2	C-OCH_3
Cyclopropyl	H	H	CH_2	C-CH_3
Cyclopropyl	C_2H_5	H	CH_2	N
Cyclopropyl	H	Br	CH_2	C-F
Cyclopropyl	H	Cl	CH_2	C-F
Cyclopropyl	H	CH_3	CH_2	C-F
Cyclopropyl	C_2H_5	NH_2	CH_2	C-F
Cyclopropyl	H	H	O	C-H
Cyclopropyl	C_2H_5	H	O	C-F
C_2H_5	H	H	O	C-Cl
CH_3	H	H	O	C-OCH_3
Cyclopropyl	H	H	O	C-CH_3
Cyclopropyl	H	H	O	N
Cyclopropyl	H	Br	O	C-F
Cyclopropyl	H	Cl	O	C-F
Cyclopropyl	H	CH_3	O	C-F
Cyclopropyl	H	NH_2	O	C-F

Acid binders which can be us d are all the customary inorganic and organic acid binding agents. These preferably include the alkali metal hydroxides, alkali metal carbonates, organic amines and amidines. Those which may be mentioned specifically as being particularly suitable are: triethylamine, 1,4-diazabicyclo-[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or excess amine (VI).

The reaction temperatures can be varied within a relatively wide range. In general the reaction is carried out between about 20 and 200°C, preferably between 80 and 180°C.

The reaction can be carried out at normal pressure, but also at elevated pressure. In general, it is carried out at pressures between about 1 and 100 bar, preferably between 1 and 10 bar.

When carrying out this process, 1 to 15 mol, preferably 1 to 6 mol of the compound (VI) are employed per mol of the compound (V).

Examples of compounds of the formula (II) which can be used both as racemates and as enantiomerically pure or diastereomerically pure compounds which may be mentioned are:

R = for xample, $(CH_3)_3C$-O,

a: H_2, Pd/A-carbon

b: acylation

c: NaH, $BrCH_2COOC_2H_5$ or c: CH_2=CH-CH_2Br, NaH,

d: $LiBH_4$ d: O_3, $NaBH_4$,

e: tosyl chloride, NEt_3,

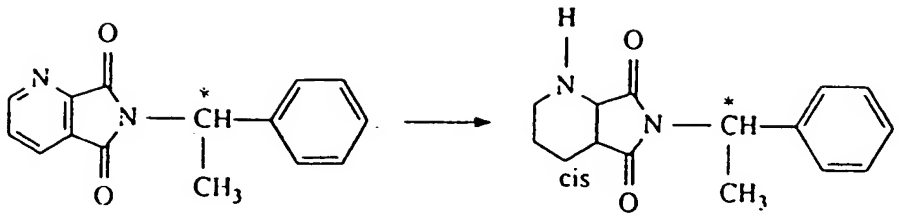
f: benzylamine, xylene, reflux

g: hydrolysis

h: H_2, Pd/A-carbon

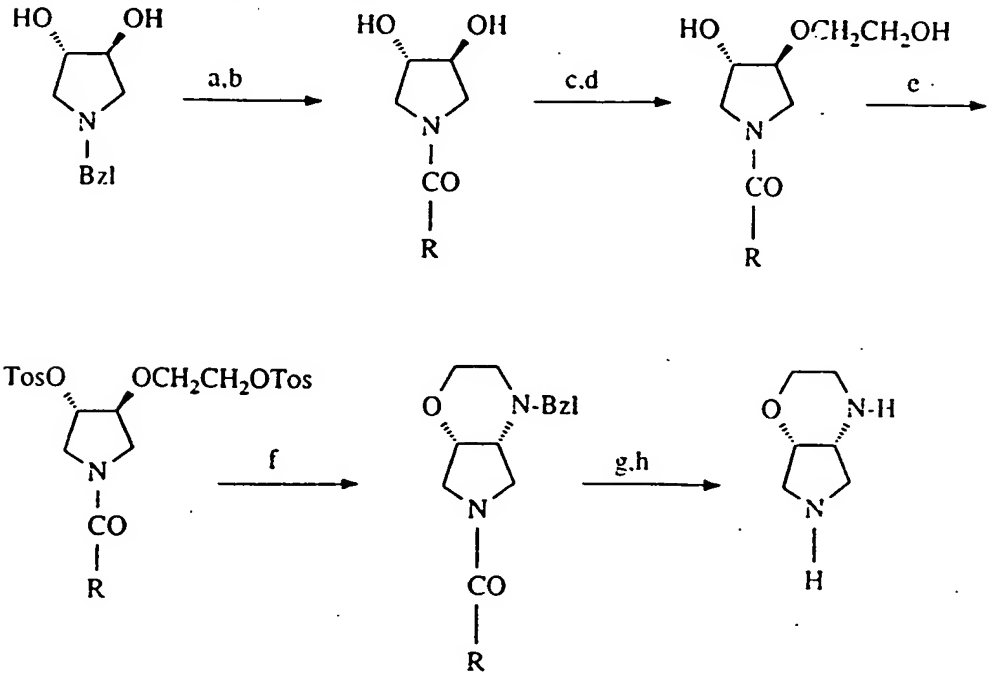
Examples of compounds of the formula (VI) which may be mentioned are:
cis-2,8-diazabicyclo[4.3.0]nonane,
cis-2-oxa-5,8-diazabicyclo[4.3.0]nonane,
trans-2-oxa-5,8-diazabicyclo[4.3.0]nonane,
S,S-2,8-diazabicyclo[4.3.0]nonane,
IR,6S-2-oxa-5,8-diazabicyclo[4.3.0]nonane,
IS,6R-2-oxa-5,8-diazabicyclo[4.3.0]nonane,
IR,6R-2-oxa-5,8-diazabicyclo[4.3.0]nonane,
IS,6S-2-oxa-5,8-diazabicyclo[4.3.0]nonane,

The reaction of (V) with (VI), in which the compounds (VI) can also be employed in the form of their salts, such as, for example, the hydrochlorides, is preferably carried out in a diluent such as dimethyl sulphoxide, N,N-dimethylformamide, N-methylpyrrolidone, hexamethylphosphoramide, sulpholane, acetonitrile, water, an alcohol such as methanol, ethanol, n-propanol or isopropanol, glycol monomethyl ether or pyridine. Mixtures of these diluents can also be used.



2.6. The enantiomerically pure amines (VI) can also be synthesised from enantiomerically pure precursors, such as, for example, [R,R]- or [S,S]-3,4-dihydroxy-pyrrolidine, which should be protected on the nitrogen by a protective group.

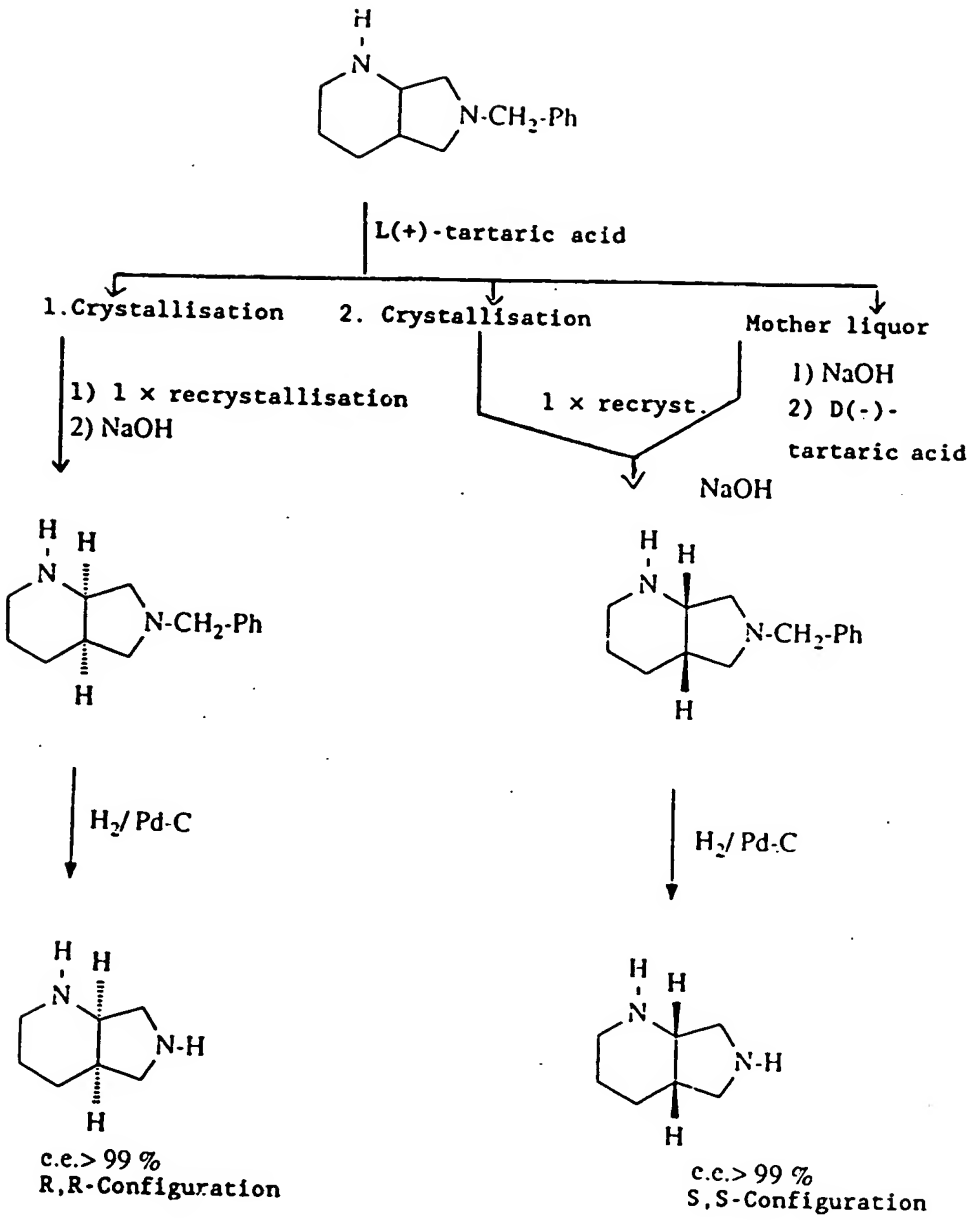
An example of the synthesis of an enantiomerically pure amine, starting from enantiomerically pure 1-benzyl-3,4-dihydroxy-pyrrolidine, which may be given is the following reaction scheme:

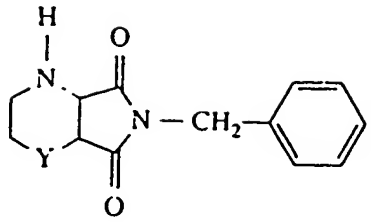


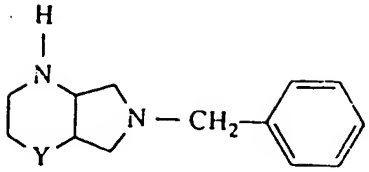
2.3. Both the racemic amines (a) and the basic intermediates (b) - (e) can be separated by chromatography, if appropriate after acylation, by means of chiral support materials (see, for example, G. Blaschke, Angew. Chem. 92, 14[1980]).

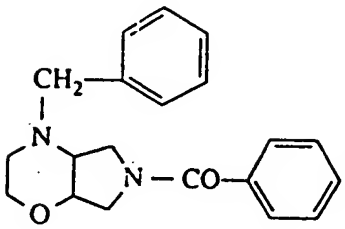
2.4. Both the racemic amines (a) and the basic intermediates (b), (c), (e) can be converted by chemical linkage with chiral acyl radicals into diastereomer mixtures which can be separated by distillation, crystallisation or chromatography into the diastereomerically pure acyl derivatives, from which the enantiomerically pure amines can be isolated by hydrolysis. Examples of reagents for linkage to chiral acyl radicals are: α-methoxy-α-trifluoromethyl-phenylacetyl chloride, menthyl isocyanate, D- or L-α-phenyl-ethyl isocyanate, menthyl chloroformate or camphor-10-sulphonyl chloride.

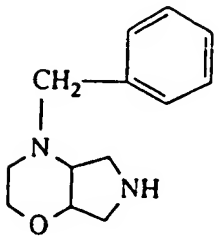
2.5. In the course of the synthesis of the bicyclic amines (a), instead of achiral protective groups chiral protective groups can also be introduced. In this manner, diastereomers are obtained which can be separated. For example, in the synthesis of cis-2,8-diazabicyclo[4.3.0]nonane, the benzyl radical can be replaced by the R- or S-α-phenylethyl radical:


L(+)-tartaric acid
1.Crystallisation
2. Crystallisation
Mother liquor
1) 1 x recrystallisation
2) NaOH
1 x recryst.
1) NaOH
2) D(-)-
tartaric acid
NaOH
H_2/ Pd-C
H_2/ Pd-C
c.e.> 99 %
R,R-Configuration
c.e.> 99 %
S,S-Configuration


(b)


(c)

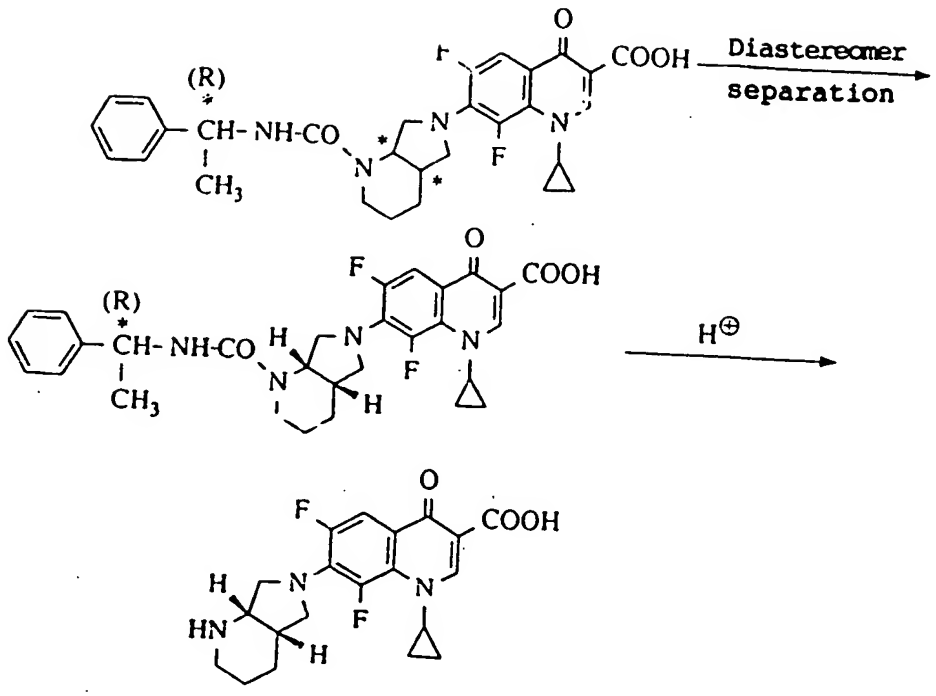

(d)


(e)

In the following reaction scheme, the separation of 8-benzyl-cis-2,8-diazabicyclo[4.3.0]nonane into the enantiomers via the tartrates and conversion thereof into the enantiomerically pure cis-2,8-diazabicyclo[4.3.0]nonanes may be shown as an example of a resolution:

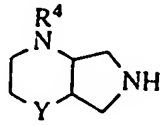
can be reacted with enantiomerically pure acids, for example carboxylic acids or sulphonic acids such as N-acetyl-L-glutamic acid, N-benzoyl-L-alanine, 3-bromocamphor-9-sulphonic acid, camphor-3-carboxylic acid, cis-camphoric acid, camphor-10-sulphonic acid, O,O'-dibenzoyl-tartaric acid, D- or L-tartaric acid, mandelic acid, α-methoxy-phenylacetic acid, 1-phenyl-ethanesulphonic acid or α-phenyl-succinic acid, to give a mixture of the diastereomeric salts, which can be separated by fractional crystallisation to give the diastereomerically pure salts (see P. Newman, Optical Resolution Procedures for Chemical Compounds, Volume 1). The molar ratio between amine and enantiomerically pure acid can be varied in a relatively wide range. By treatment of these salts with alkali metal or alkaline earth metal hydroxides, the enantiomerically pure amines can be liberated.

2.2. In a similar manner, as described in 2.1., resolution of the basic intermediates which occur during the preparation of the racemic bicyclic amines can be carried out using the abovementioned enantiomerically pure acids. Examples of basic intermediates of this type are:



2. The bicyclic amines (VI) are, as enantiomerically pure compounds, new. They can be prepared by the following processes:

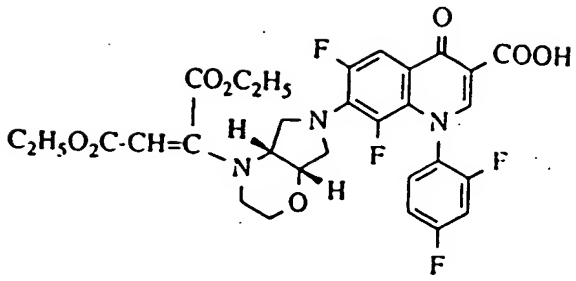
2.1. The racemic bicyclic amines (a)



(a)

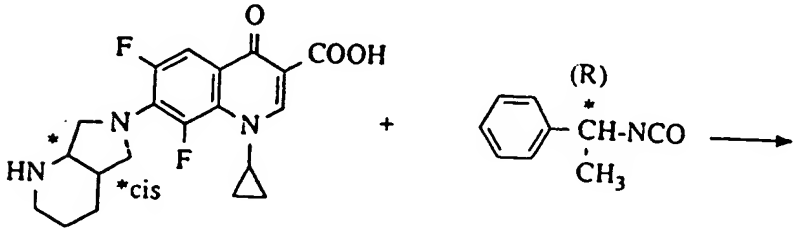
in which

R^4 represents H or C_1-C_3-alkyl,

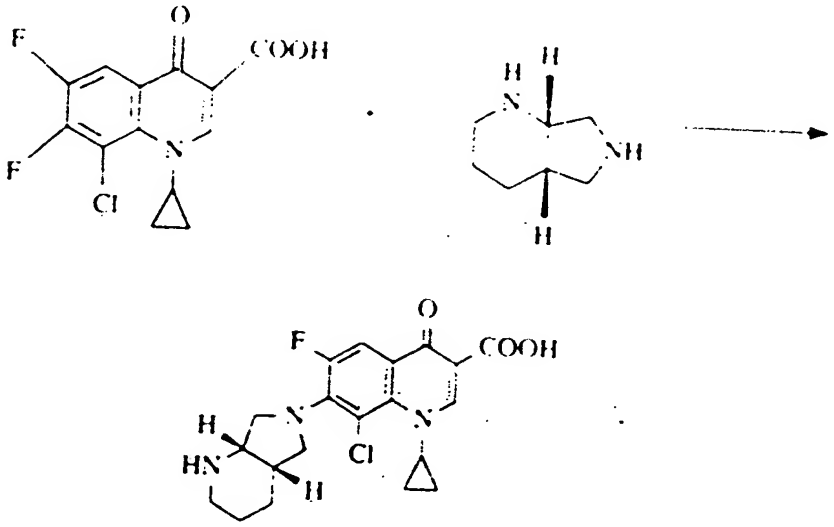


The racemic compounds of the formula (II) used as starting compounds are mainly known. Enantiomerically pure compounds of the formula (II) are new and can be obtained in various ways.

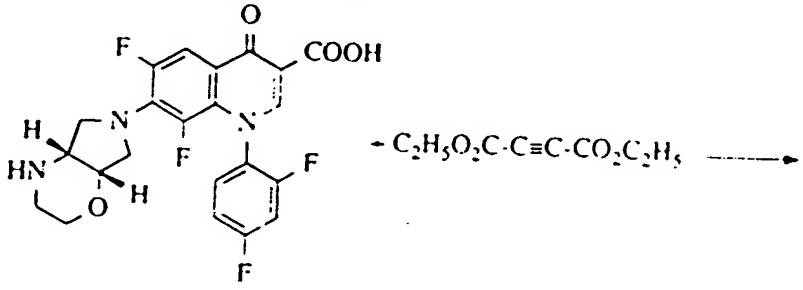
1. A racemic intermediate of the formula (II) is reacted with an enantiomerically pure auxiliary reagent, the resulting diastereomers are separated, for example by chromatography and the chiral auxiliary group is removed again from the desired diastereomer. The following reaction may be shown as an example:



diazabicyclo[4.3.0]nonane are used as starting compounds, the course of the reaction can be represented by the following reaction scheme:



If, for example, 6,8-difluoro-1-(2,4-difluorophenyl)-1,4-dihydro-7-([1S,6R)-2-oxa-5,8-diazabicyclo[4.3.0]non-8-yl)-4-oxo-3-quinolinecarboxylic acid and diethyl acetylenedicarboxylate are used as starting substances, the course of the reaction can be represented by the following reaction scheme:



if appropriate in the presence of acid scavengers,

and the reaction product is optionally further reacted with a compound of the formula (IIIa)

$$R^4\text{-}X^3 \qquad \text{(IIIa)}$$

in which

X^3 has the abovementioned meaning and

R^4 represents C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, $CH_2CH_2CO_2R'$ or CH_2CH_2-CN,

in which

R' denotes hydrogen or C_1-C_3-alkyl,

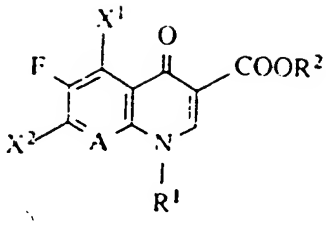
or with a Michael acceptor such as dialkyl acetylenedicarboxylate, alkyl propiolate or a compound of the formula (IV)

$$CH_2{=}CH\text{-}R^5 \qquad \text{(IV)}$$

in which

R^5 represents $COCH_3$, CO_2R' or CN [Method C].

If, for example, 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid and [S,S]-2,8-



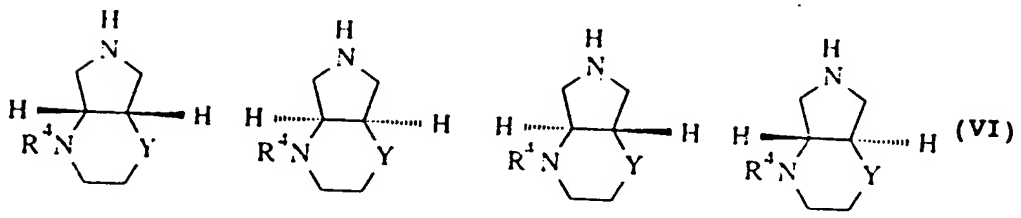
(V)

in which

A, R^1, R^2 and X^1 have the abovementioned meaning and

X^2 represents halogen, in particular fluorine or chlorine,

is reacted with enantiomerically pure compounds of the formulae (VI)



(VI)

in which

Y represents O or CH_2 and

R^4 represents H or C_1-C_3-alkyl,

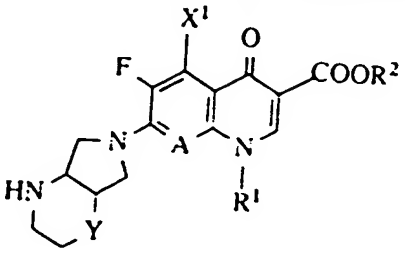
$R'O_2C-CH=C-CO_2R'$, $-CH=CH-CO_2R'$ or CH_2CH_2-CN,

in which

R' denotes hydrogen or C_1-C_3-alkyl,

can be obtained

by reacting a compound of the formula (II)



(II)

with a Michael acceptor such as dialkyl acetylenedicarboxylate, alkyl propiolate or a compound of the formula (IV)

$$CH_2=CH-R^5 \qquad (IV)$$

in which

R^5 represents $COCH_3$, CO_2R' or CN. [Method B]

To prepare enantiomerically pure compounds of the formula (I), a compound of the formula (V)

R^3 represents C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, CH_2CH_2-CO_2R' or CH_2CH_2-CN,

in which

R' denotes hydrogen or C_1-C_3-alkyl, and

X^3 represents halogen, in particular chlorine, bromine or iodine,

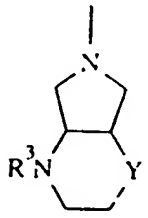
if appropriate in the presence of acid binders. [Method A]

Compounds according to the invention of the formula (I)

in which

A, X^1, R^1 and R^2 have the abovementioned meaning, and

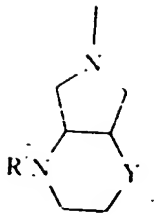
B represents a radical of the formula



in which

Y has the abovementioned meaning and

R^3 represents CH_2CH_2-CO-CH_3, CH_2CH_2-CO_2R',

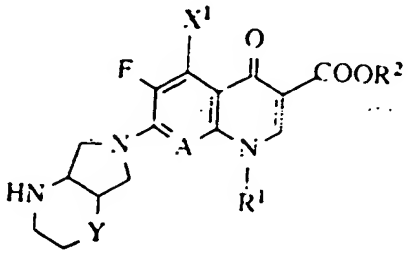


in which

R^3 and Y have the abovementioned meaning,

are obtained

by reacting a compound of the formula (II)



(II)

in which

A, Y, X^1, R^1 and R^2 have the abovementioned meaning,

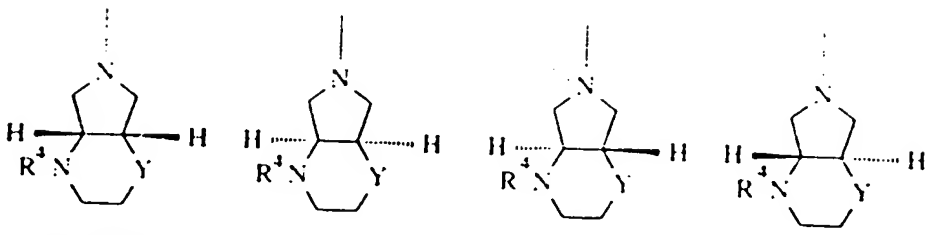
with a compound of the formula (III)

$$R^3\text{-}X^3 \qquad \text{(III)}$$

in which

R^2 represents H, CH_3 or C_2H_5,

B represents a radical of the formulae



in which

Y represents O or CH_2 and

R^4 represents H, C_1-C_3-alkyl, 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl, CH_2-CO-CH_3, CH_2-CO-C_6H_5, CH_2CH_2-CO-CH_3, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C(CO_2R')-, -CH=CH-CO_2R' or CH_2CH_2-CN,

in which

R' denotes C_1-C_2-alkyl.

The compounds of the formula (I)

in which

A, X^1, R^1 and R^2 have the abovementioned meaning, and

B represents a radical of the formula

Y represents O or CH_2 and

R^3 represents CH_2-CO-CH_3, CH_2-CO-C_6H_5, CH_2CH_2-CO-CH_3, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C(CO_2R')-, -CH=CH-CO_2R' or CH_2CH_2-CN,

in which

R' denotes C_1-C_2-alkyl.

R^4 represents H, C_1-C_3-alkyl, 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl, CH_2-CO-CH_3, CH_2-CO-C_6H_5, CH_2CH_2-CO-CH_3, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C(CO_2R')-, -CH=CH-CO_2R' or CH_2CH_2-CN,

in which

R' denotes C_1-C_2-alkyl.

Particularly preferred compounds of the formula (I) are those in which

A represents CH, CF, CCl, C-OCH_3 or N,

X^1 represents H, F, Cl, Br, NH_2 or CH_3,

R^1 represents C_2H_5, cyclopropyl or 2,4-difluorophenyl, or A and R^1 together can denote a bridge of the structure C-O-CH_2-$CH(CH_3)$-,

and to pharmaceutically utilisable hydrates and acid addition salts thereof as well as the alkali metal, alkaline earth metal, silver and guanidinium salts of the underlying carboxylic acids. These compounds have a high antibacterial activity. The compounds according to the invention are particularly distinguished in that they have a high activity on dormant and resistant microorganisms.

Preferred compounds of the formula (I) are those in which

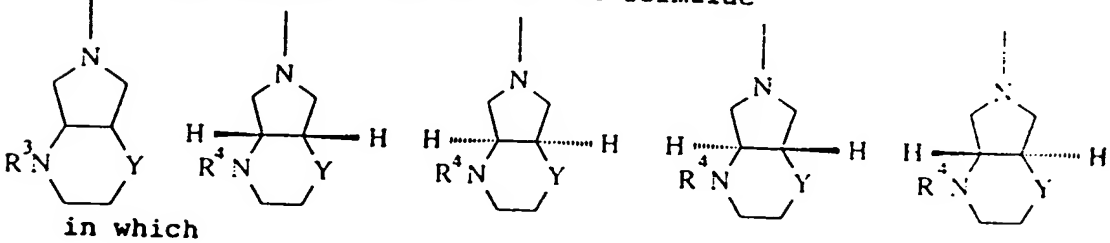
A represents CH, CF, CCl, C-OCH_3 or N,

X^1 represents H, F, Cl, Br, NH_2 or CH_3,

R^1 represents C_2H_5, cyclopropyl or 2,4-difluorophenyl, or A and R^1 together can denote a bridge of the structure C-O-CH_2-$CH(CH_3)$-,

R^2 represents H, CH_3, C_2H_5 or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

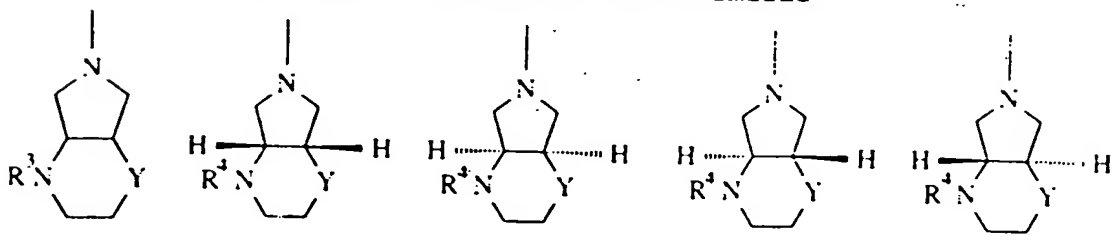
B represents a radical of the formulae



in which

R^2 represents H, C_1-C_3-alkyl which is optionally substituted by hydroxyl, halogen or amino or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

B represents a radical of the formulae



in which

Y represents O or CH_2,

R^3 represents C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C(CO_2R')-CO_2R', -CH=CH-CO_2R' or CH_2CH_2-CN,

in which

R' denotes hydrogen or C_1-C_3-alkyl,

R^4 represents H, C_1-C_3-alkyl, C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, $CH_2CH_2CO_2R'$, $R'O_2C$-CH=C(CO_2R')-CO_2R', -CH=CH-CO_2R' or CH_2CH_2-CN or represents 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

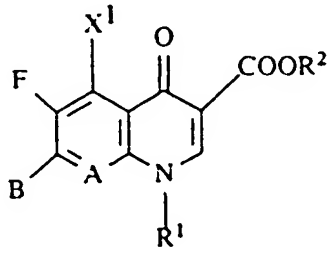
in which

R' denotes hydrogen or C_1-C_3-alkyl,

The invention relates to new quinolone- and naphthyridonecarboxylic acid derivatives, processes for their preparation and also antibacterial agents and feed additives containing them.

Quinolone- and naphthyridonecarboxylic acids which are substituted in the 7-position by a bicyclic amine radical have already been disclosed in EP-A-0,350,733.

The present invention relates to new compounds of the formula (I)



(I)

in which

A represents CH, CF, CCl, C-OCH_3, C-CH_3 or N,

X^1 represents H, halogen, NH_2 or CH_3,

R^1 represents C_1-C_3-alkyl, FCH_2CH_2-, cyclopropyl or phenyl which is optionally monosubstituted to trisubstituted by halogen, or A and R^1 together can denote a bridge of the structure C-O-CH_2-$CH(CH_3)$-,

Quinolone- and naphthyridone-carboxylic acid derivatives

2066314

ABSTRACT OF THE DISCLOSURE

The invention relates to new quinolone- and naphthyridone carboxylic acid derivatives, processes for their preparation and also antibacterial agents and feed additives containing them.

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Consumer and Corporate Affairs Canada

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Patent Office

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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Quinolone-and Naphthyridone-Carboxylic Acid Derivatives

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(DE) P 42 08 792.9 1992/03/19

(57) 14 Claims